理論家が考えていること

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このチュートリアルの内容

はじめに

- モデル化する、解析的に解く、数値的に解く
- 微分方程式とは
- **縮約とは**

具体例I: 生化学反応

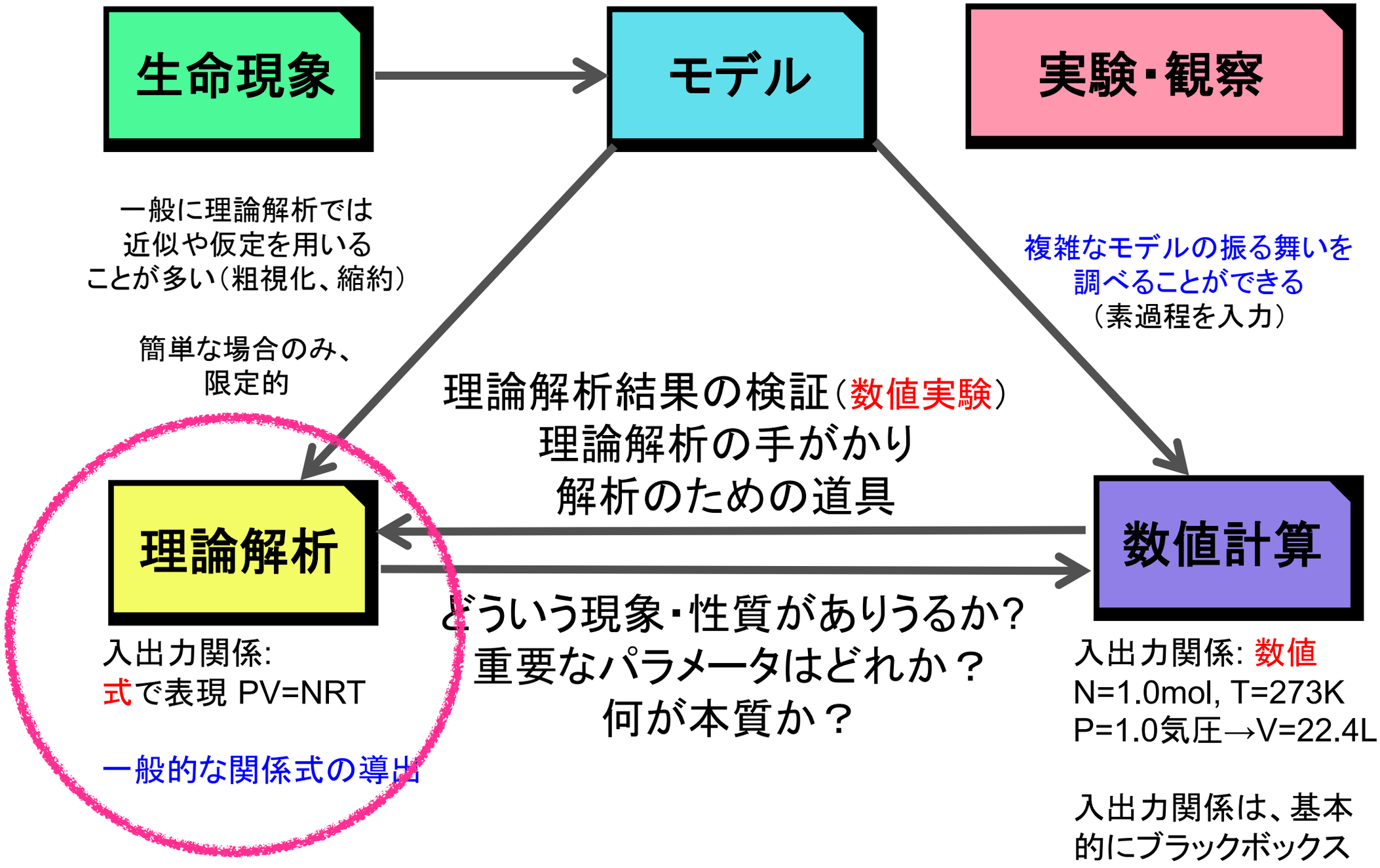
具体例2:神経の興奮

メッセージ

- 理論と実験の幸せな関係(郡)
- それで実験生物学者は何をするべき？(伊藤)

前回の杉村さん+石原さんのチュートリアルのスライドお借りしました。

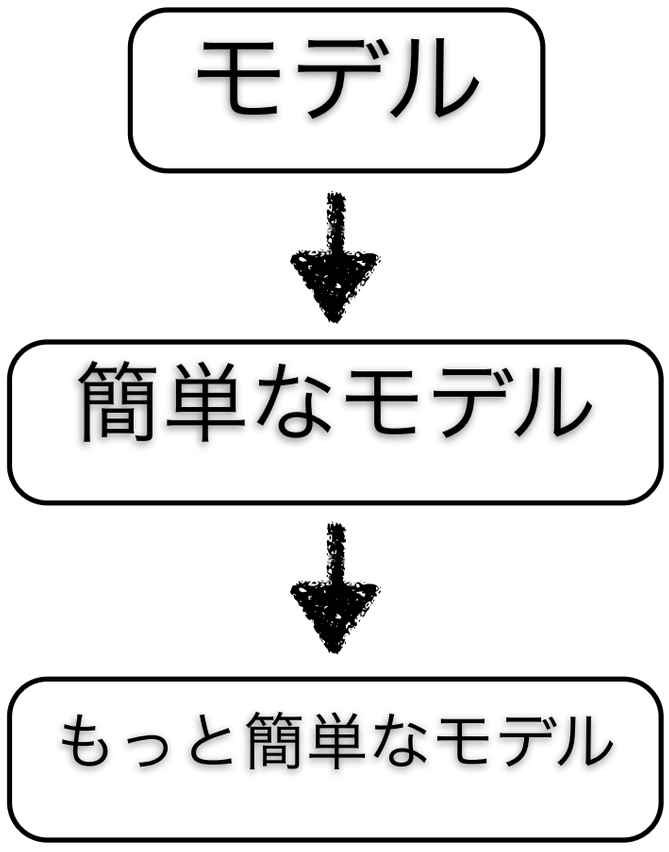
理論研究のフレームワーク（地図）



ここ重点的にお話しします。杉村・石原　定量生物2 理論チュートリアル

縮約とは？

モデルを簡単にすること。



縮約すると、　**わかる　とける　遊べる**

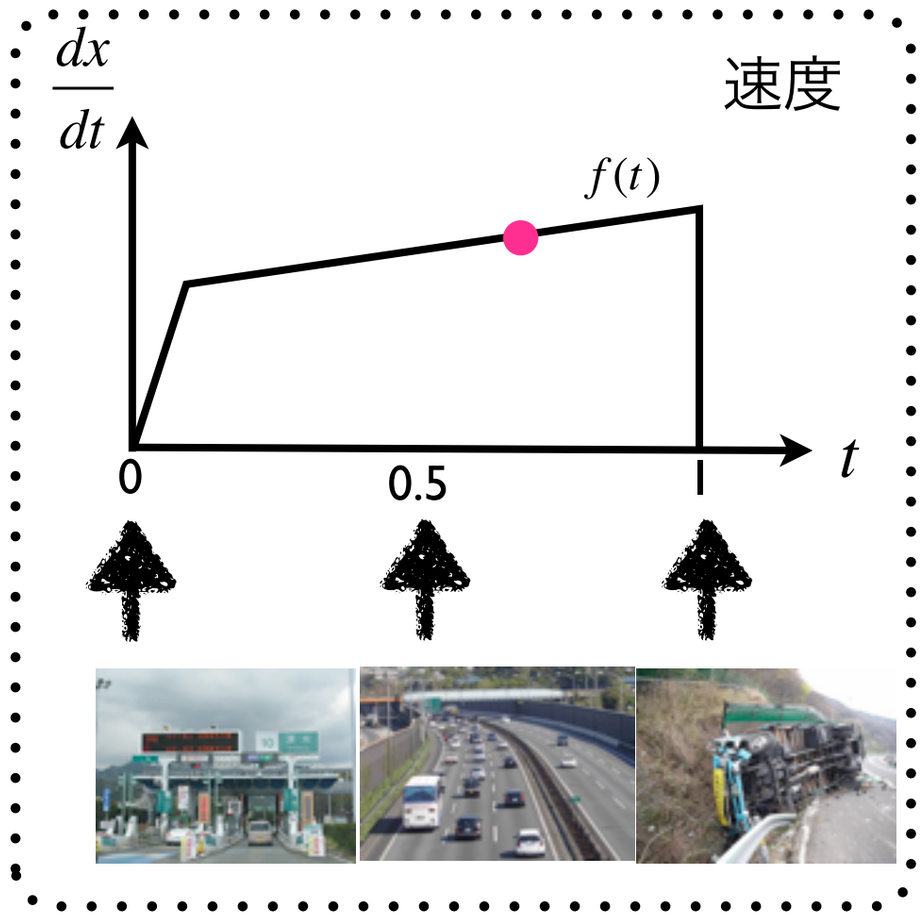
これらの意味はプレゼンテーションが終わる頃には理解されている、はず

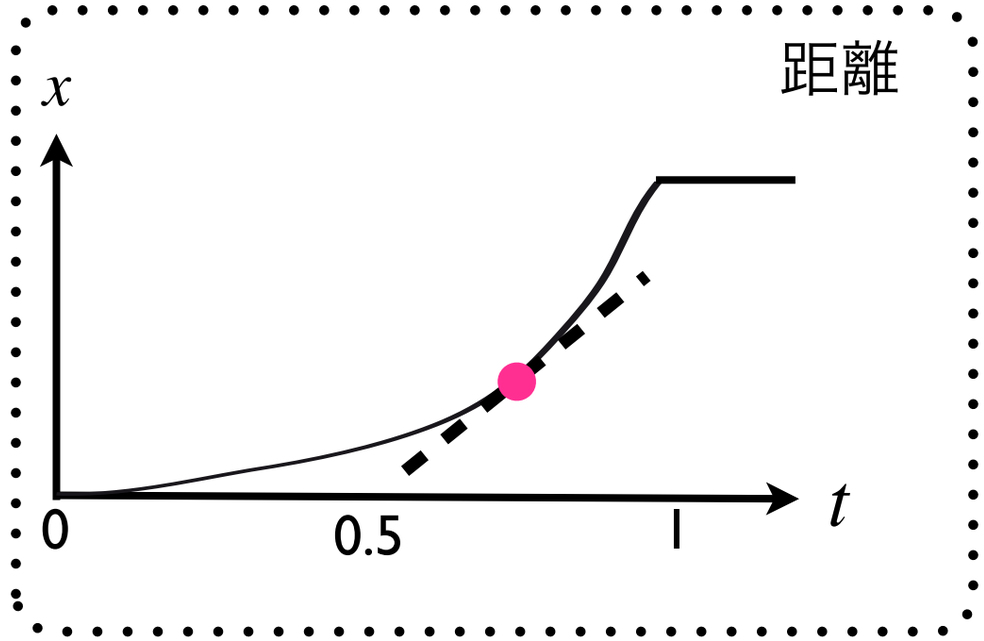
自然のダイナミクス(時間変化)は微分方程式で表される

微分方程式がこれからたくさんでてきます。

じっくり見れば、怖くない！

例:車のダイナミクス



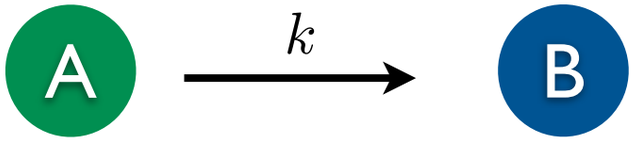


$$\frac{dx}{dt} = f(t)$$

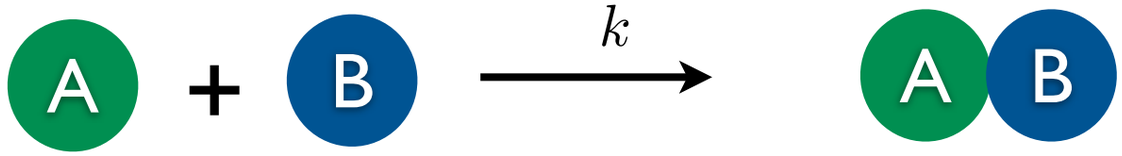
自然のダイナミクスは微分方程式で表した方が
シンプルに表現できることが多い。

具体例1:生化学反応

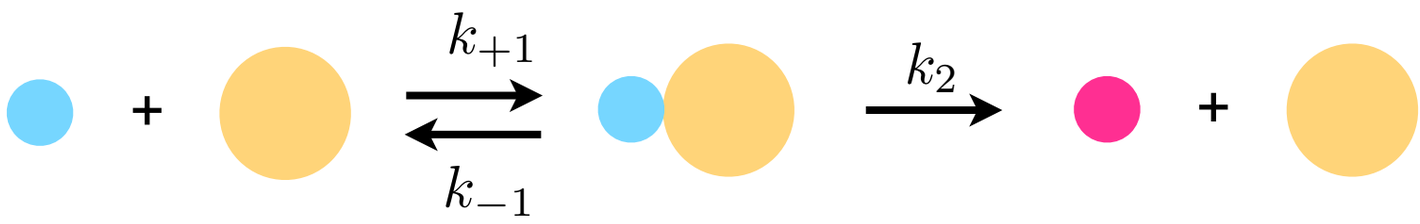
- LEVEL1: 分解反応



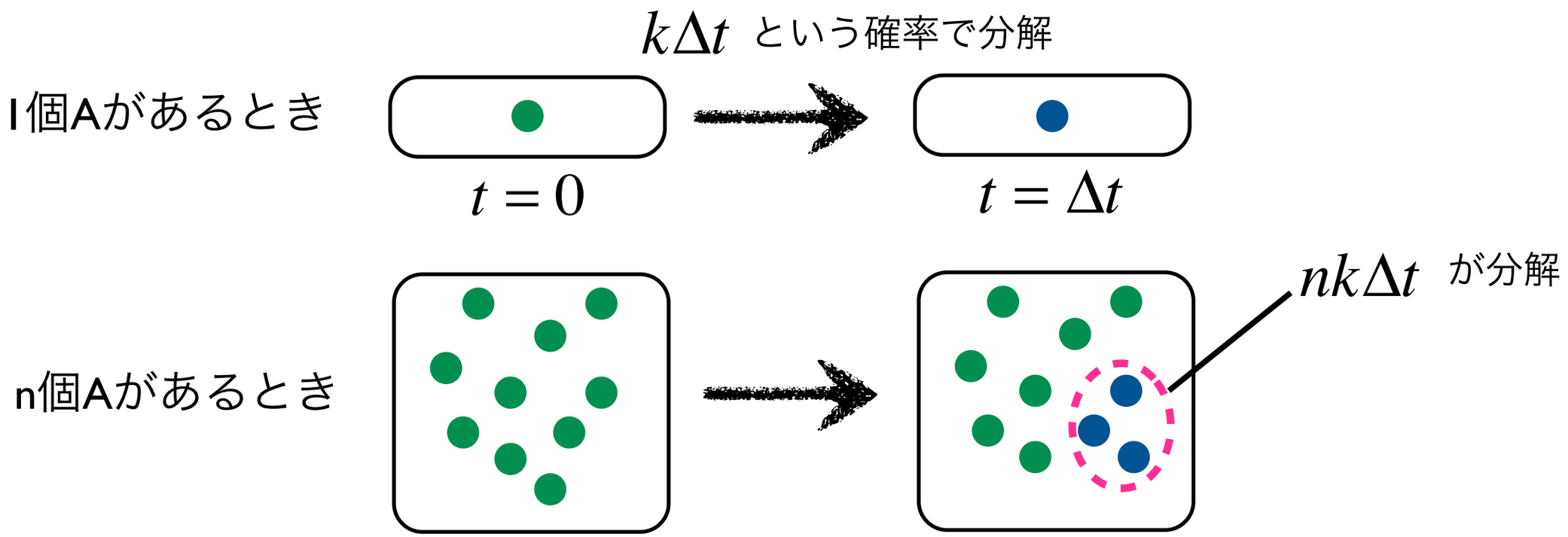
- LEVEL2:複合体形成反応



- LEVEL3:酵素反応



LEVEL 1:分解反応



まず、モデル化

$$\Delta n = -nk\Delta t$$

(Δtを移項)

$$\frac{\Delta n}{\Delta t} = -nk$$

(Δt→0の極限を取った)

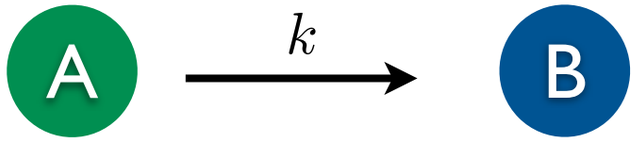
$$\frac{dn}{dt} = -nk$$

(個数÷体積=濃度)

モデル

$$\frac{d[A]}{dt} = -k[A]$$

LEVEL 1:分解反応



モデル化が済んだら解を求める

$$\frac{d[A]}{dt} = -k[A]$$

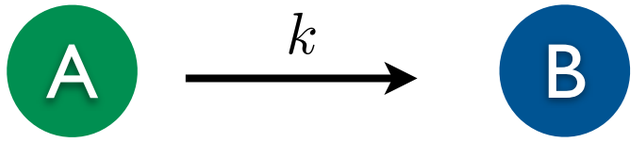
モデル

この微分方程式の解析解は…？

“変数”とパラメータ

$$A(t) = ?$$

LEVEL 1:分解反応



モデル化が済んだら解を求める

$$\frac{d[A]}{dt} = -k[A]$$

モデル

この微分方程式の解析的な解は...？

$$A(t) = A(0)e^{-kt}$$

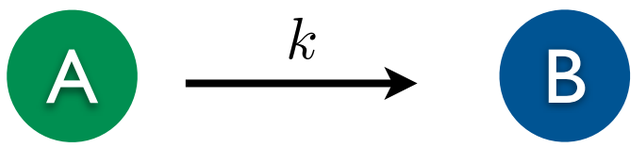
解析解

初めて知った！という方は一緒に検算してみましょう。

$$(\text{左辺}) \quad = -kA(0)e^{-kt}$$

$$(\text{右辺}) \quad = -kA(0)e^{-kt}$$

LEVEL 1:分解反応



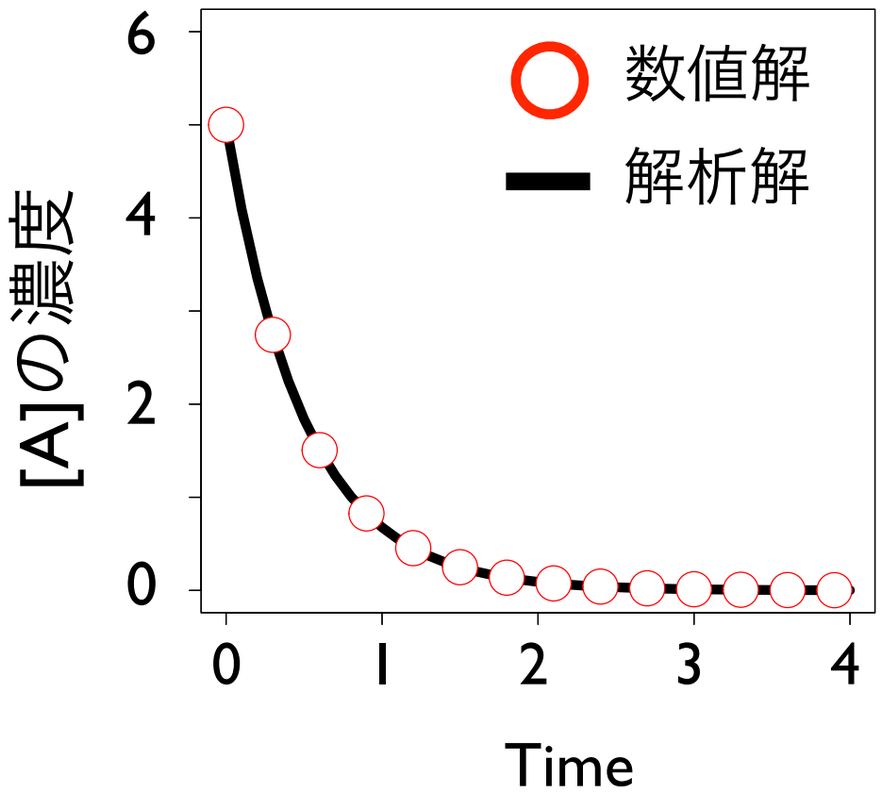
$$\frac{d[A]}{dt} = -k[A]$$

モデル

$$A(t) = A(0)e^{-kt}$$

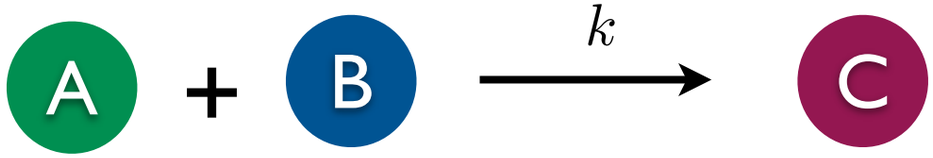
解析解

数値計算(シミュレーション)で確認してみます。



数値解

質量作用の法則

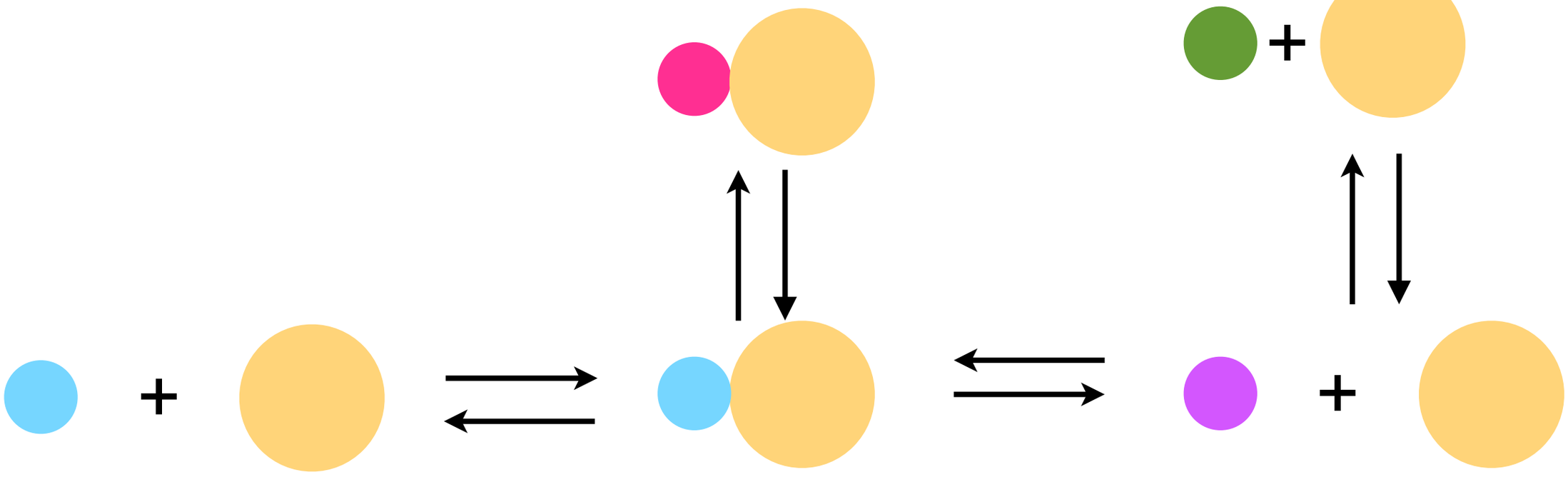


$$\frac{d[C]}{dt} = k[A][B]$$

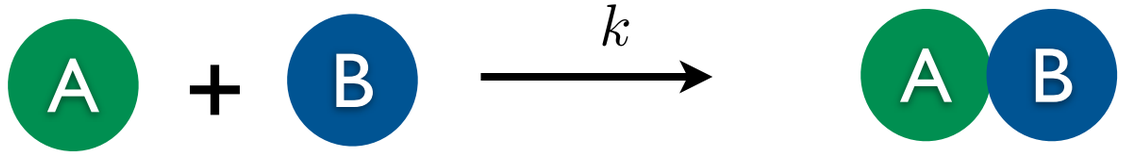
Cの合成レート

(質量作用の法則)

質量作用の法則に従えば、複雑に見える
化学反応も誰でも**モデル化**できます。



LEVEL2:複合体形成反応

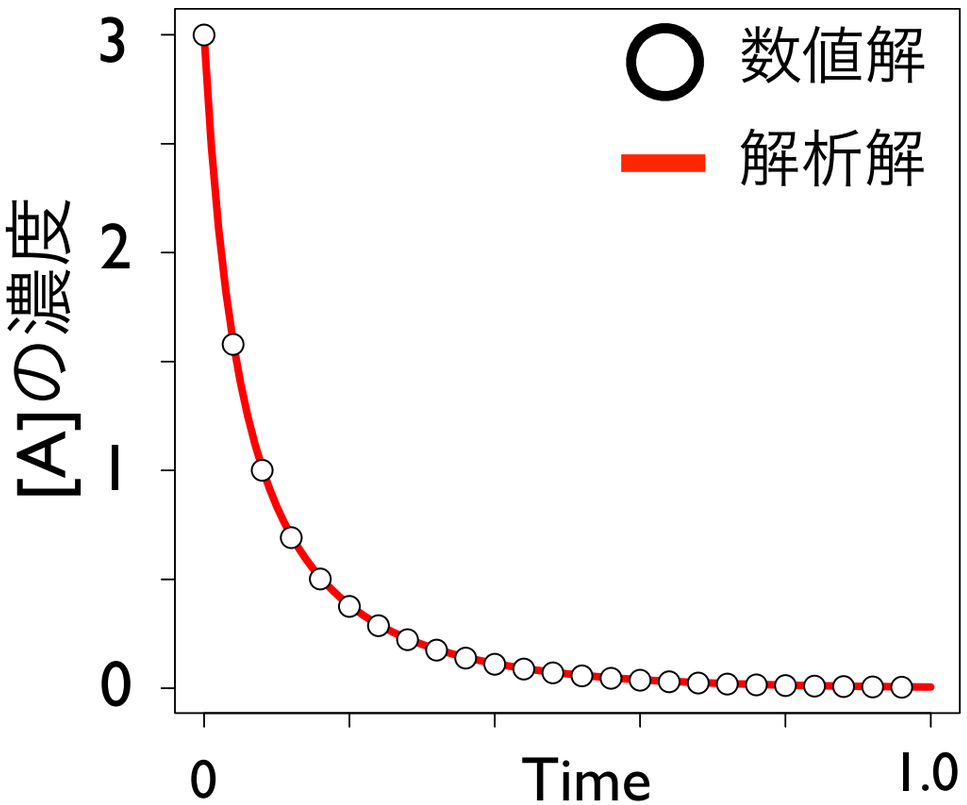


$$\frac{dA}{dt} = -kAB$$

$$\frac{dB}{dt} = -kAB$$

モデル

※濃度の[ ]を以後省略します



$k = 5$

$A(0) = 3, B(0) = 4$

解析解を求めてみよう。

$\frac{dB}{dt} - \frac{dA}{dt} = 0$ より $B - A = c$ を得る。

代入して得られる $\frac{dA}{dt} = -kA(c + A)$

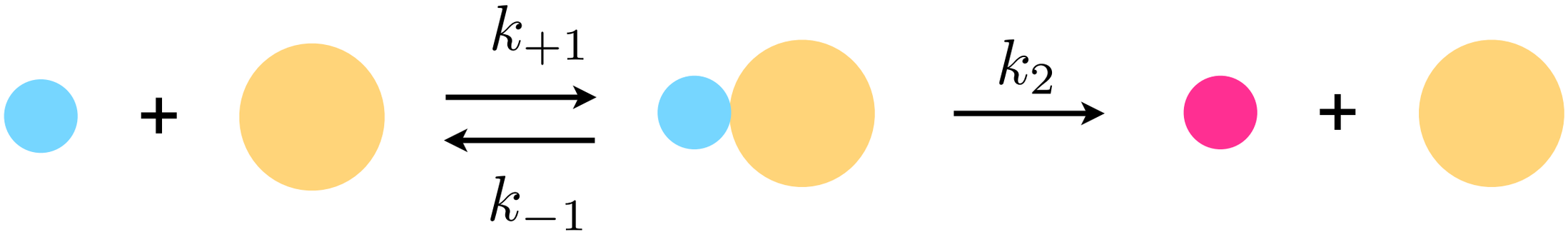
という微分方程式を解くと、

$A = \frac{c}{\alpha e^{kct} - 1}$ ただし、$\alpha = \frac{c}{A(0)} + 1$

解析解

数値解

LEVEL3:酵素反応



登場人物 4人

酵素	E	デヒドロゲナーゼ
基質	S	アセトアルデヒド
生成物	P	酢酸
複合体	C	デヒドロゲナーゼ-アルデヒド複合体

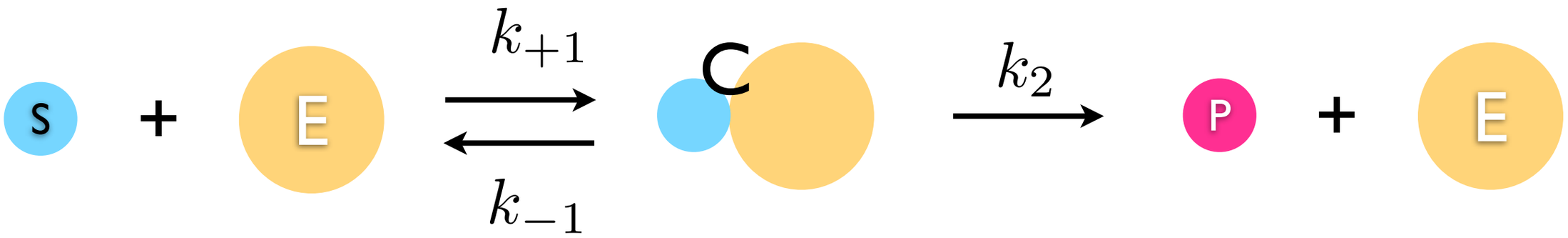
具体例

Micahelise-Mentenの関係式

(1912)

$$\frac{dP}{dt} = \frac{k_{\max} S}{S + k_m}$$

質量作用の法則から定式化する



S

$$\frac{dS}{dt} = -k_{+1}SE + k_{-1}C$$

E

$$\frac{dE}{dt} = -k_{+1}SE + k_{-1}C + k_2C$$

C

$$\frac{dC}{dt} = k_{+1}SE - k_{-1}C - k_2C$$

P

$$\frac{dP}{dt} = k_2C$$

とりあえず数値計算してみる

モデル

$$\frac{dS}{dt} = -k_{+1}SE + k_{-1}C$$

$$\frac{dE}{dt} = -k_{+1}SE + k_{-1}C + k_2C$$

$$\frac{dC}{dt} = k_{+1}SE - k_{-1}C - k_2C$$

$$\frac{dP}{dt} = k_2C$$

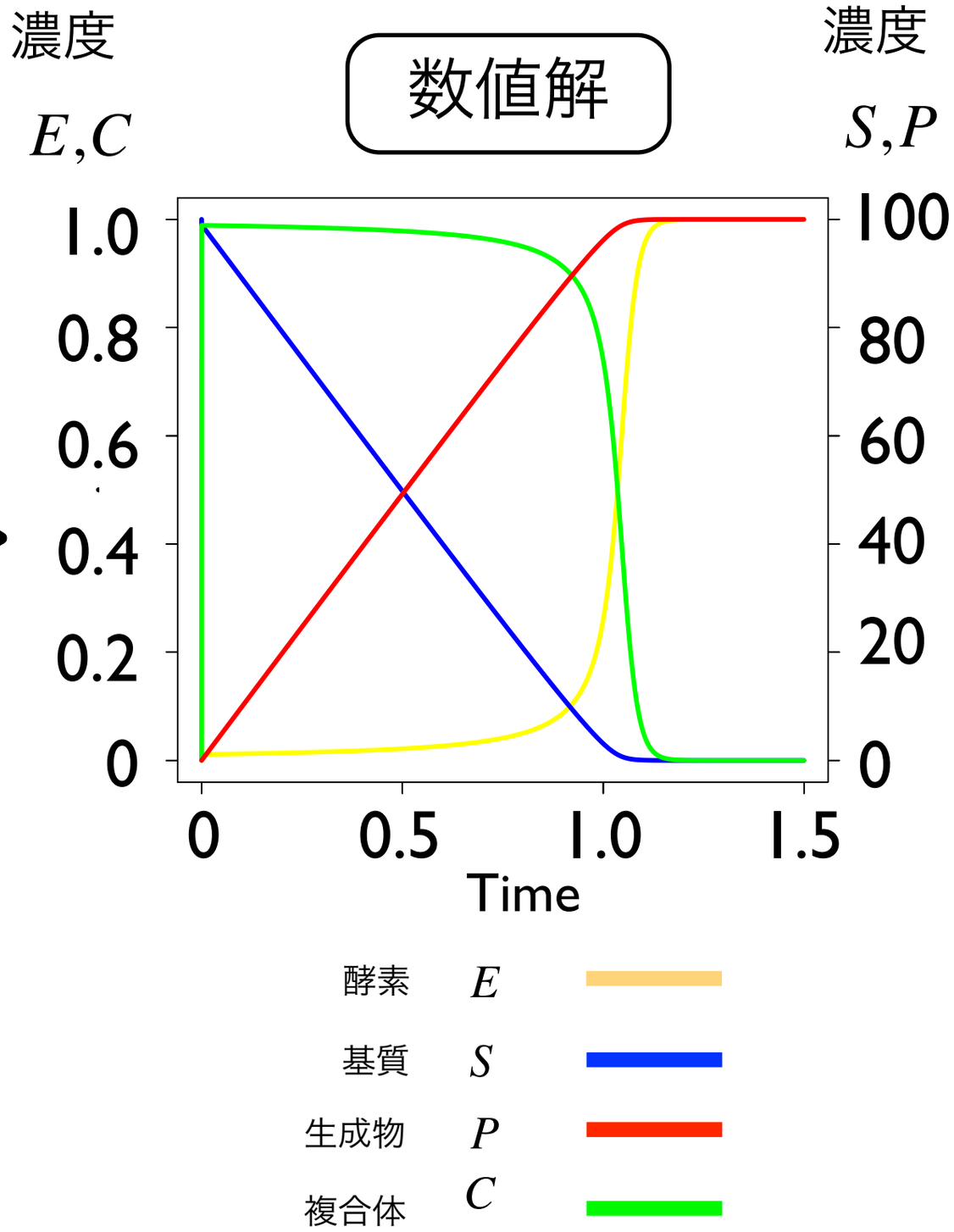
パラメータ

$$k_{+1} = 1, k_{-1} = 1, k_2 = 0.1$$

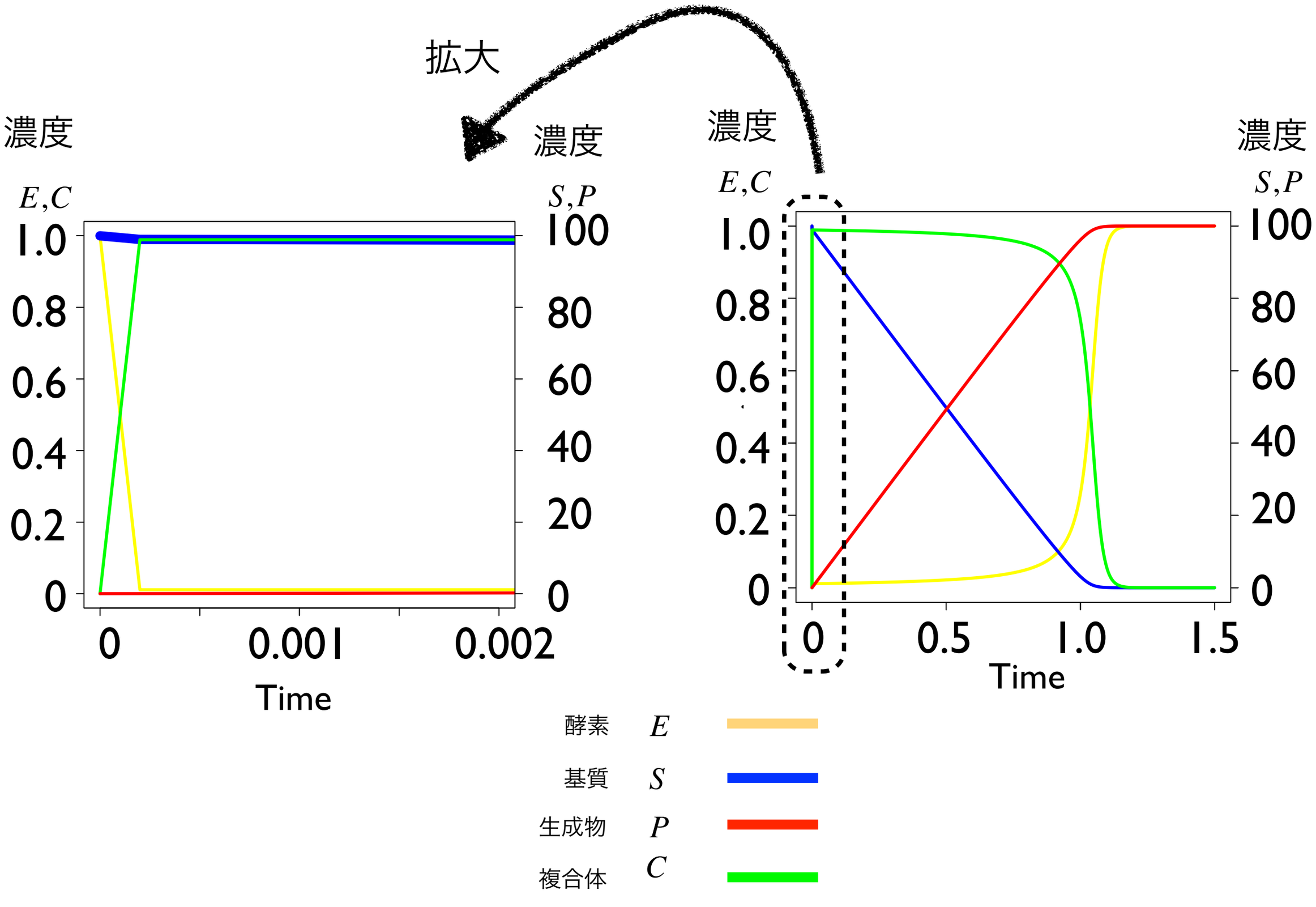
$$E(0) = 1, S(0) = 100, C(0) = 0, P(0) = 0$$

(★)

数値解



数値計算結果をもう少し味わってみる



4次元から2次元へ

システムをよく見てみると、

① Pは右辺に出てこないので(iv)は不要 (生成物はダイナミクスに寄与しない)

② $\frac{dE}{dt}+\frac{dC}{dt}=0$ より $E+C=E_0$ (酵素は消費されない)

(i) $\frac{dS}{dt}=-k_{+1}SE-k_{-1}C$

(ii) $\frac{dE}{dt}=-k_{+1}SE+k_{-1}C+k_2C$

(iii) $\frac{dC}{dt}=k_{+1}SE-k_{-1}C-k_2C$ (★)

(iv) $\frac{dP}{dt}=k_2C$

(i) $\frac{dS}{dt}=-k_{+1}S\left(E_0-C\right)+k_{-1}C$

(iii) $\frac{dC}{dt}=k_{+1}S\left(E_0-C\right)-k_{-1}C-k_2C$ (●)

- EはE+C=E_0から求めれば良い
- PはCを積分すればよい

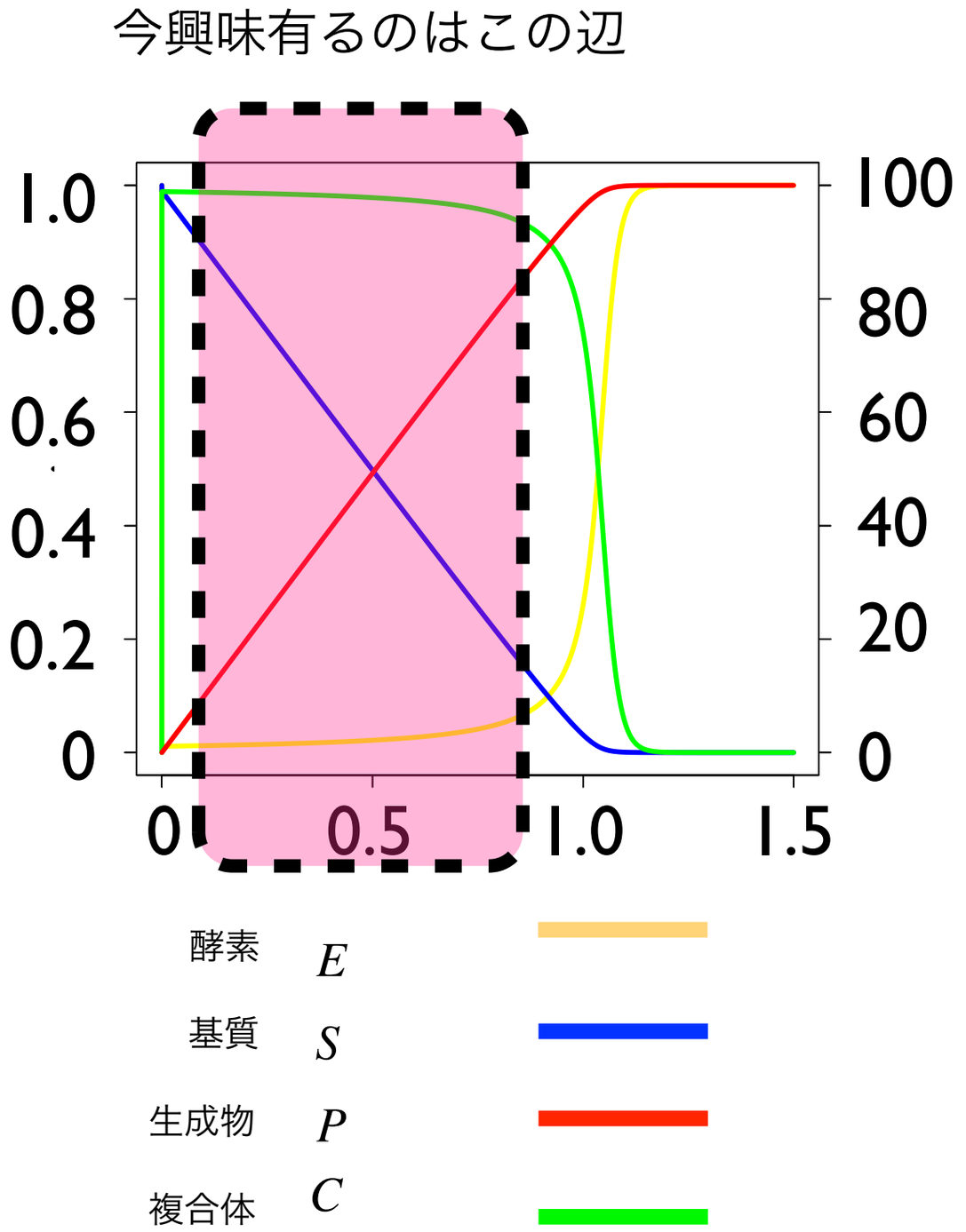
もっと簡単にするために

何を知りたいのか？を考える

- 知りたいのは生成物の合成速度。特に基質がたくさんあって、リニアに増えている時刻のあたり

- 複合体やフリーの酵素の量は観測が難しいので、基質の量と生成物の合成速度を関係づけたい。(質量作用の法則が破れているように見えるのはなぜ？)

ヒント：基質と複合体を比べたら、
複合体の変化は速そう。



もっと簡単に、一次元に縮約

今考えているシステム

$$\text{(i)}\quad \frac{dS}{dt} = -k_{+1}S\left(E_0 - C\right) + k_{-1}C$$

$$\text{(ii)}\quad \frac{dC}{dt} = k_{+1}S\left(E_0 - C\right) - k_{-1}C - k_2 C \qquad (\bullet)$$

手順1: 変数変換

$$\left(t, S, C\right) \to \left(\tau, x, y\right)$$

手順2: 断熱消去で1変数消去

$$\left(\tau, x, y\right) \to \left(\tau, y\right)$$

縮約後のシステム

$$\frac{dy}{d\tau} = -\frac{qy}{y+\kappa} \qquad (※)$$

手順I:変数変換

今考えているシステム

$$\text{(i)}\quad \frac{dS}{dt} = -k_{+1}S\left(E_0 - C\right) + k_{-1}C$$

$$\text{(ii)}\quad \frac{dC}{dt} = k_{+1}S\left(E_0 - C\right) - k_{-1}C - k_2 C \qquad (\bullet)$$

無次元化された量に
変数変換

$$\tau = k_{+1}E_0 t$$

$$x = \frac{C}{E_0}$$

$$y = \frac{S}{S_0}$$

今から”大きさ”の比較をするので、
次元があると比較できない。
CとSがだいたい同じ大きさに
なるように規格化

変数変換後のシステム

$$\text{(i)}\quad \varepsilon\frac{dx}{d\tau} = y - x(y+\kappa)$$

$$\text{(ii)}\quad \frac{dy}{d\tau} = -y + x(y+\alpha) \qquad (\circ)$$

ただし、ε,κ, αは定数

$$\varepsilon = \frac{E_0}{S_0}, \kappa = \frac{k_{-1}+k_2}{k_1 S_0}, \alpha = \frac{k_{-1}}{k_{+1}S_0}$$

手順2:断熱消去

変数変換後のシステム

$$\text{(i)}\quad \frac{dx}{d\tau} = \frac{y - x(y+\kappa)}{\varepsilon}$$

$$\text{(ii)}\quad \frac{dy}{d\tau} = -y + x(y+\alpha)$$

ただし、ε,κ, αは定数

$$\varepsilon = \frac{E_0}{S_0}, \kappa = \frac{k_{-1}+k_2}{k_1 S_0}, \alpha = \frac{k_{-1}}{k_{+1} S_0} \qquad (\circ)$$

さてここで、基質E_0がS_0に比べてとても少ない状況を考える。

この生物学的な知識を利用して(○)からI変数消してみよう。

εがとっても小さい(0.001ぐらい)としたら....

さて、この仮定の下で速い変数は, x, yのうちどっち？

答え:xが速い、yが遅い。

一応、数値計算で確認しておきます。

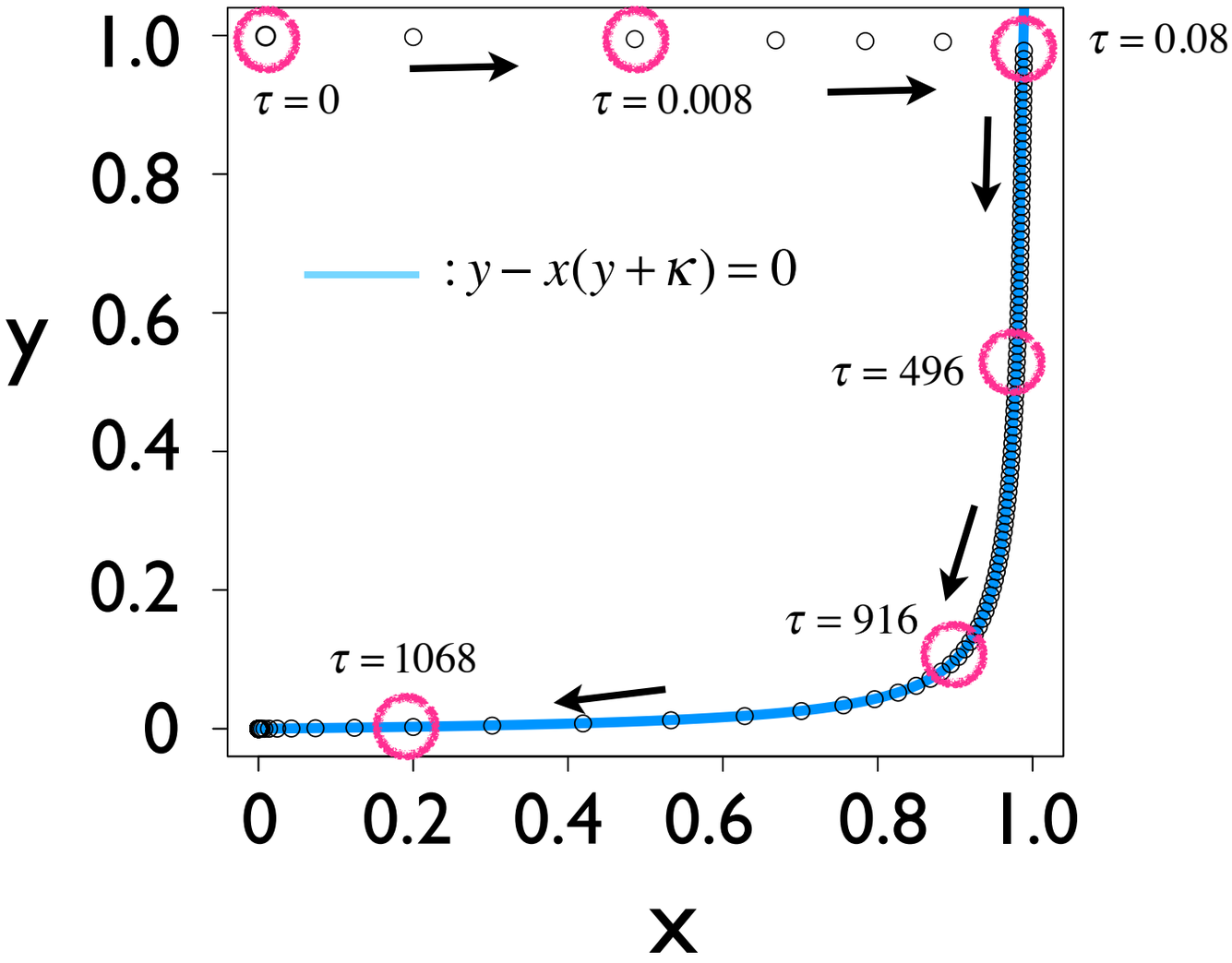
(i) $\varepsilon \dfrac{dx}{d\tau} = y - x(y+\kappa)$

(ii) $\dfrac{dy}{d\tau} = -y + x(y+\alpha)$

ただし、ε,κ, αは定数

$\varepsilon = \dfrac{E_0}{S_0}, \kappa = \dfrac{k_{-1}+k_2}{k_1 S_0}, \alpha = \dfrac{k_{-1}}{k_{+1} S_0}$ (○)

(○)の数値計算結果



$\varepsilon \dfrac{dx}{d\tau} = 0$ すなわち、

$y - x(y+\kappa) = 0$ が成り立つ曲線上に

最初以外は常に束縛されている。

というわけで、最終的に1次元に

(i) $y - x(y+\kappa) = 0$　　ただし、ε,κ, αは定数

(ii) $\dfrac{dy}{d\tau} = -y + x(y+\alpha)$　　$\varepsilon = \dfrac{E_0}{S_0}, \kappa = \dfrac{k_{-1}+k_2}{k_1 S_0}, \alpha = \dfrac{k_{-1}}{k_{+1} S_0}$　　(○')

yだけで、まとめると、

$$\frac{dy}{d\tau} = -\frac{qy}{y+\kappa}$$

ただし、ε,κ, αは定数

$\kappa = \dfrac{k_{-1}+k_2}{k_1 S_0}, \alpha = \dfrac{k_{-1}}{k_{+1} S_0}, q = \kappa - \alpha$　　(※)

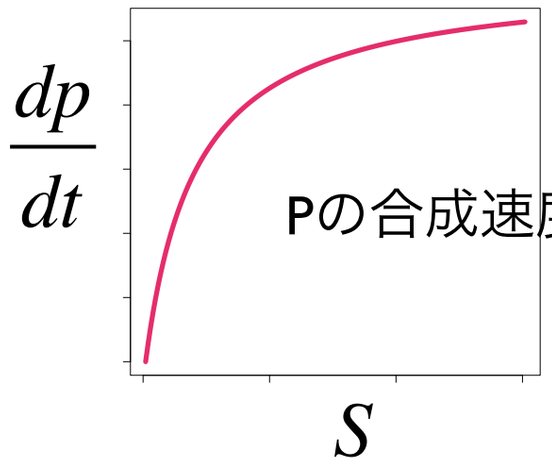
この微分方程式、幸い**手で解けます**(書きくだすとごちゃごちゃした式)。

ちなみに、$y - x(y+\kappa) = 0$ は、CとSを関係づける式→ $C = \dfrac{SE_0}{S + S_0\kappa}$

これから生物学的に重要な結果

$$\frac{dP}{dt} = k_2 C = \frac{k_2 E_0 S}{S + S_0\kappa} = \frac{k_{cat} S}{S + k_m}$$

Micahelise-Mentenの関係式 (1912)



Pの合成速度はSが多いと比例しない

ここまでのまとめ

生化学反応は質量作用の法則を適用すれば、モデル化できる。

酵素反応は、基本的には4変数のしんどい系。でも縮約したら、1変数の解けるレベルまで簡単になった。

しかも、副産物として、生物学的に嬉しいミカエリス-メンテンの式が導出出来た。

具体例２：神経の興奮

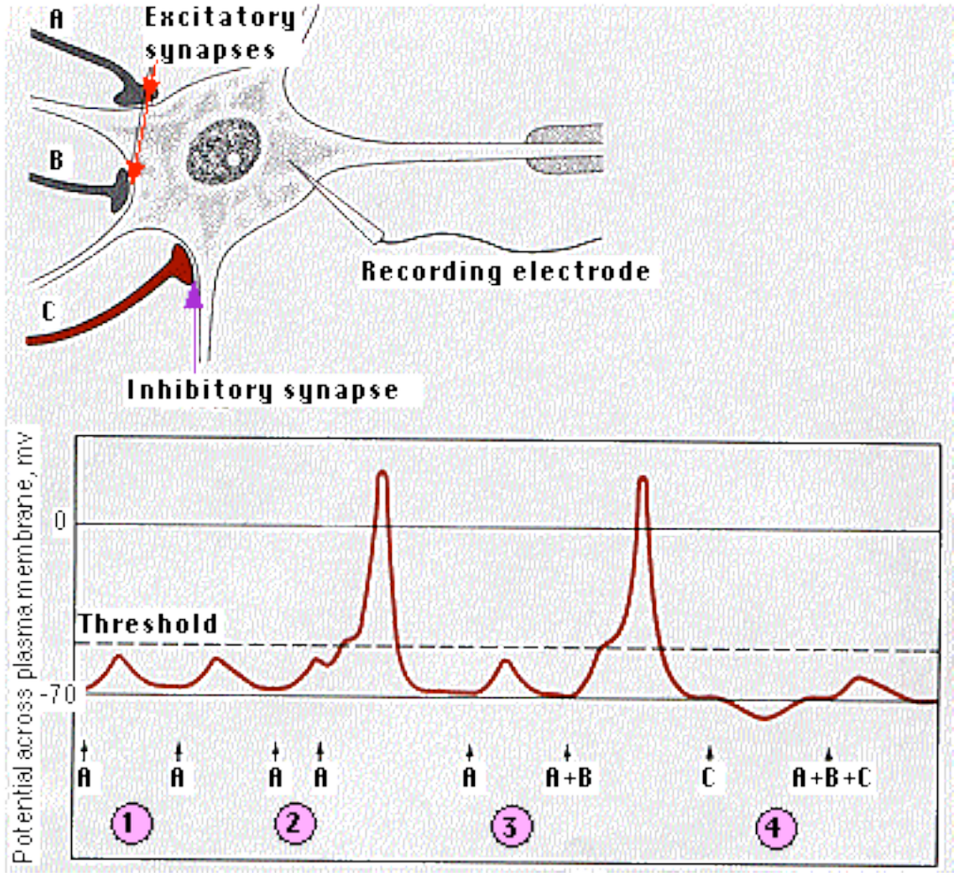
「縮約」

イカ、わかる、広がる、遊べる

HodgkinとHuxleyの研究 (1952)

神経興奮の「メカニズム」を解明

神経興奮とは？



・閾値の存在

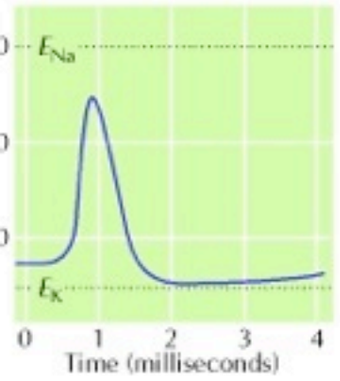
・スパイクがでる

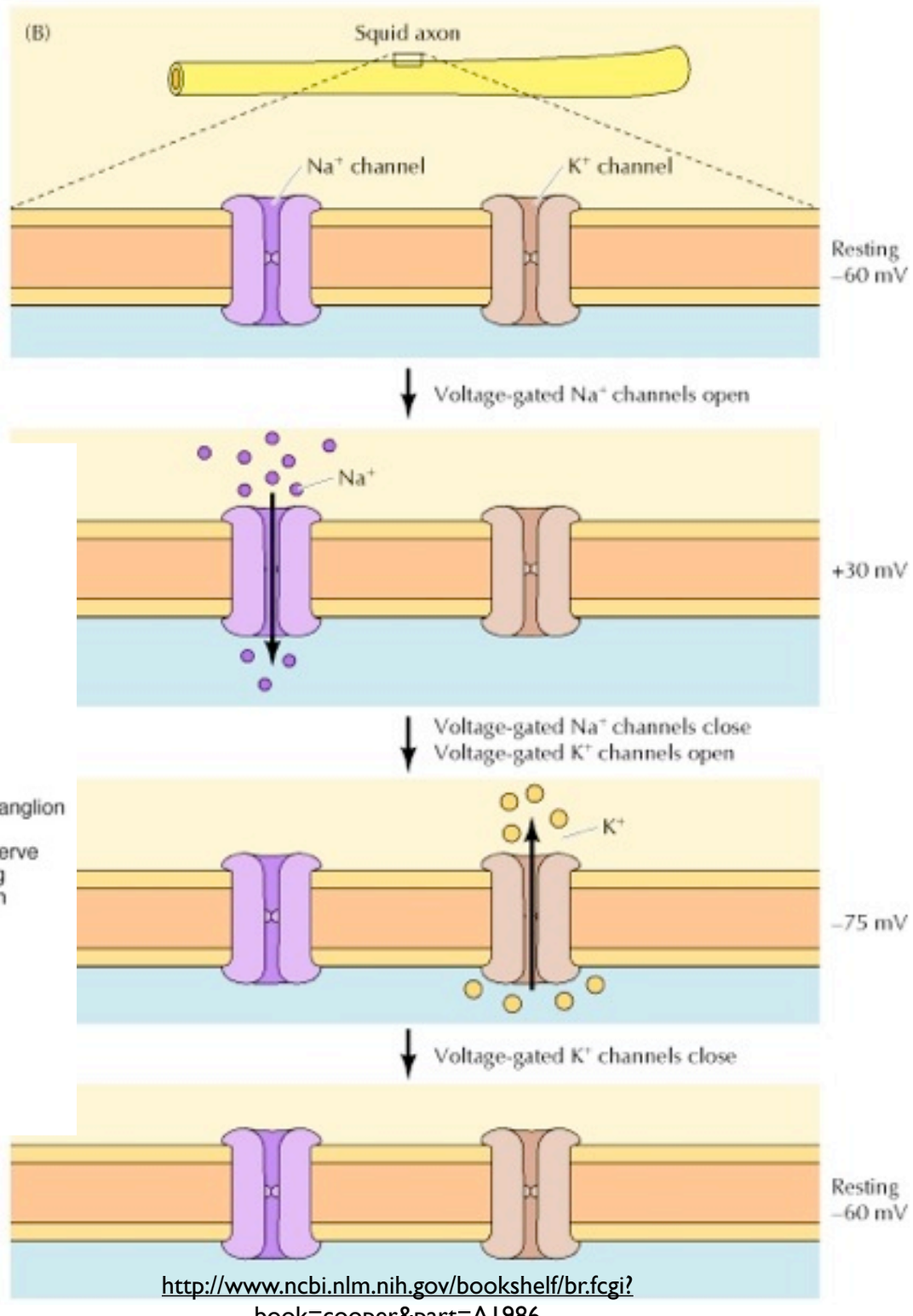
（入力よりも大きな応答）

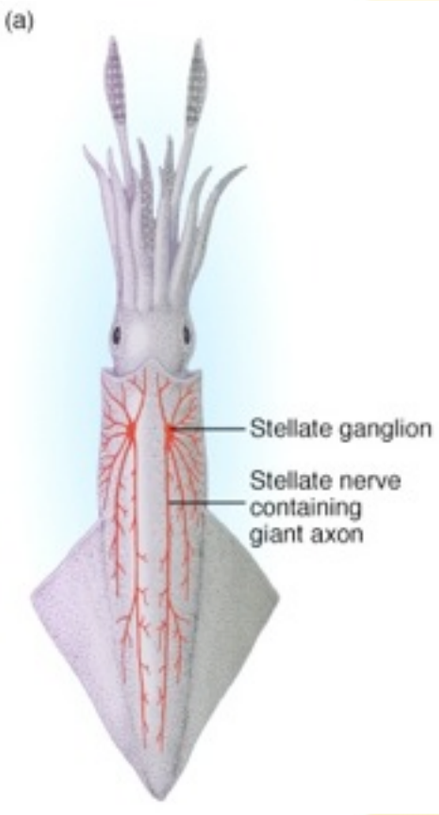
興奮性(excitable)と呼ばれる。

神経細胞の興奮のメカニズムはなんぞや？

HodgkinとHuxleyのしたこと







http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=cooper&part=A1986

(i) いくつかのイオンチャネルの性質が膜電位にどう依存するかを実験的に定量（パーツに分解）

(ii) 観測結果とつじつまが合うようにパーツごとに数理モデルを構成（再構成）

(iii) モデルの数値解析によって神経興奮が現れることを実証（動いた！）

ノーベル医学・生理学賞！(1962)

Hodgkin-Huxleyモデルの全体像

４変数の微分方程式

$$C\frac{dV}{dt} = I_L + I_K + I_{Na} + I_{ext}$$

$$\frac{dn}{dt} = \frac{f_n(V) - n}{\tau_n(V)}$$

$$\frac{dm}{dt} = \frac{f_m(V) - m}{\tau_m(V)}$$

$$\frac{dh}{dt} = \frac{f_h(V) - h}{\tau_h(V)}$$

V: 膜電位

C: 電気容量

I: 電流

n,m,h：開いたチャネルの割合

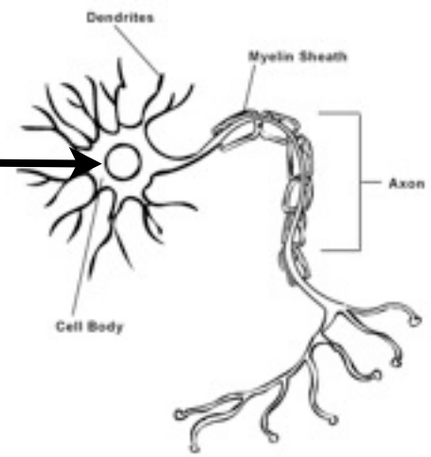
$f_?, \tau_?$： とある関数

パーツごとに説明

膜電位の従う基本方程式

電流

（プラスイオンの流れ）



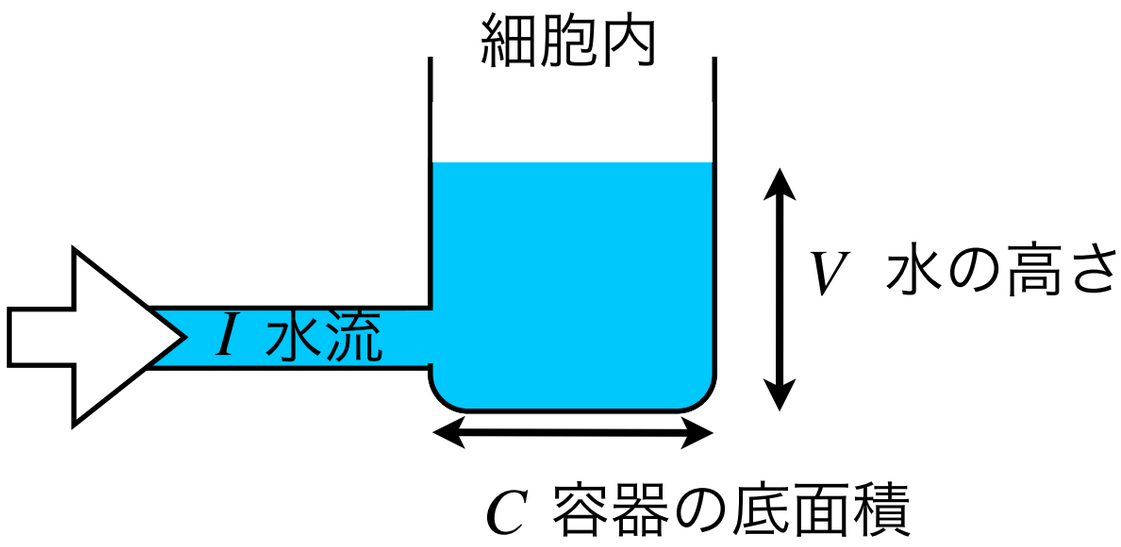
基本方程式

$$C\frac{dV}{dt} = I$$

V: 膜電位

C: 電気容量

I: 電流



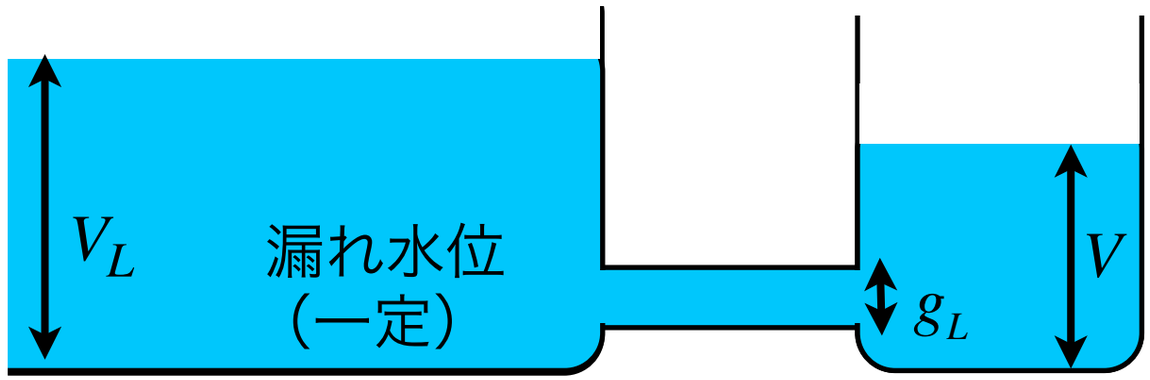
$$\frac{dV}{dt} = \frac{I}{C}$$

漏れ(Leak)電流

$$C\frac{dV}{dt} = I_L + I_K + I_{Na} + I_{ext}$$

漏れ電流の式

$$I_L = g_L(V_L - V)$$

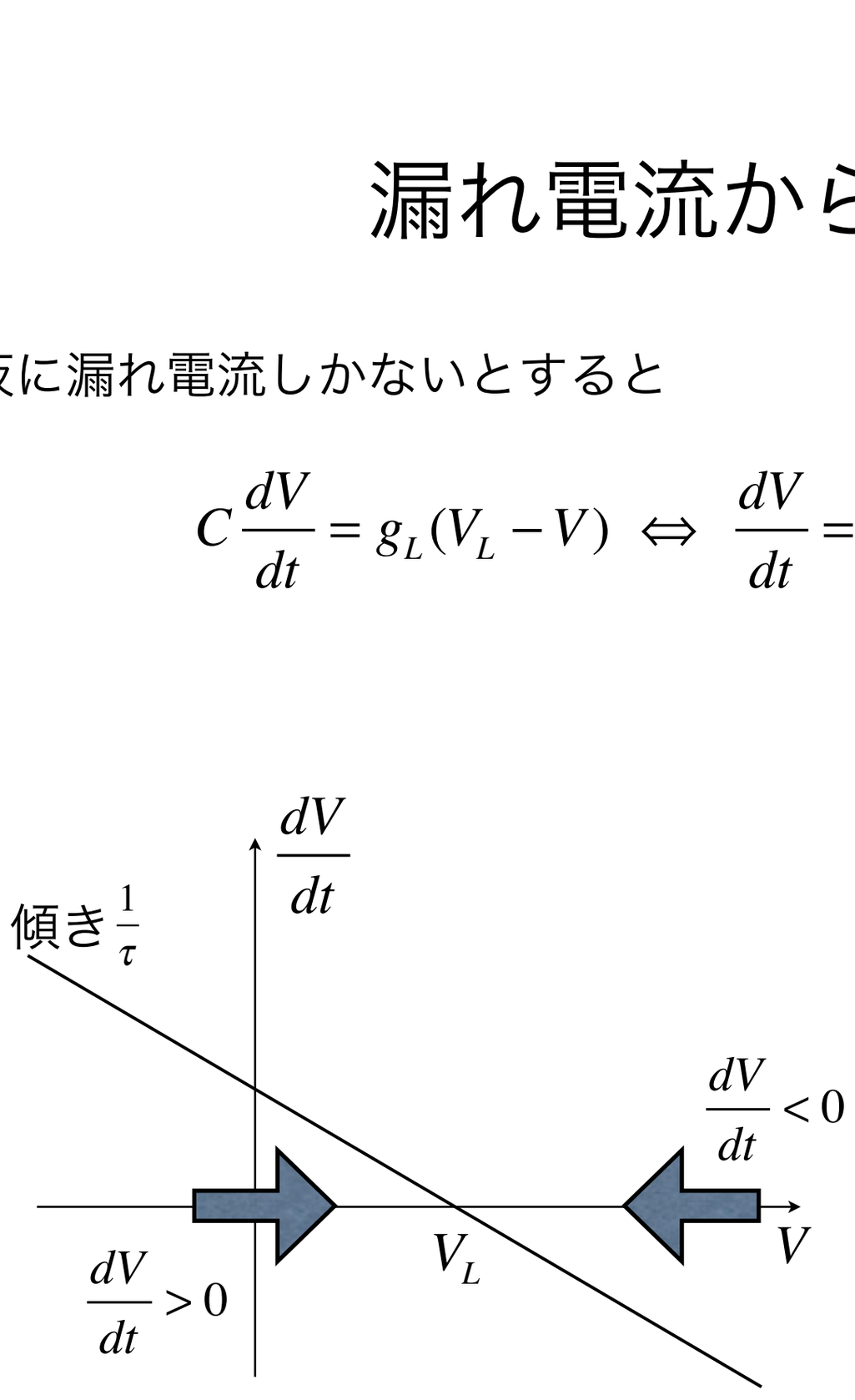


g_L パイプの面積

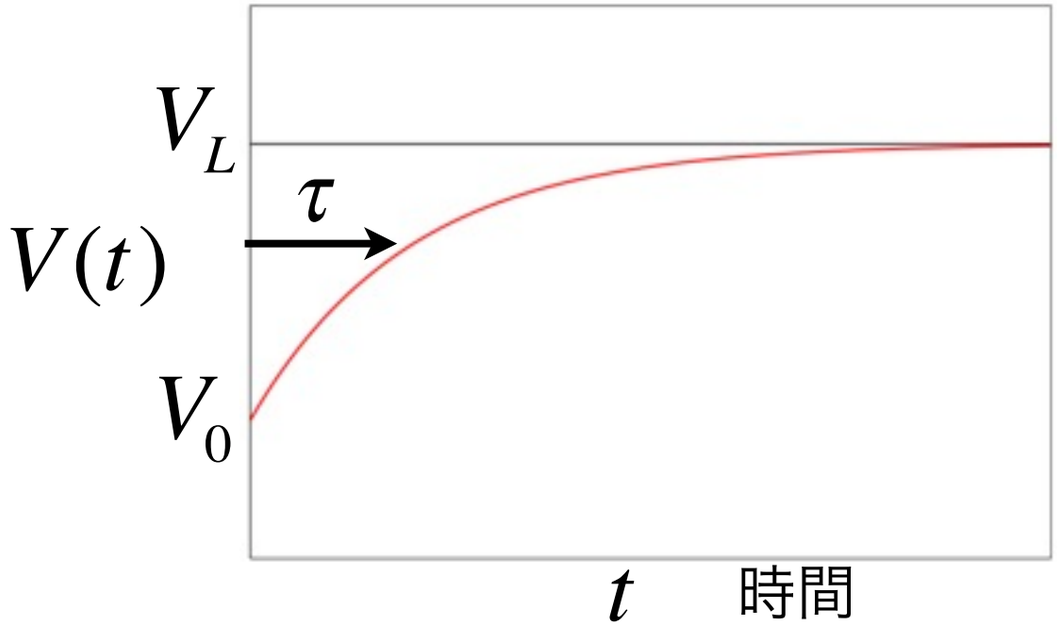
漏れ電流から見る緩和の数学

仮に漏れ電流しかないとすると

$$C\frac{dV}{dt} = g_L(V_L - V) \Leftrightarrow \frac{dV}{dt} = \frac{V_L - V}{\tau} \qquad \left(\tau = \frac{g_L}{C}\right)$$



解　$V(t) = V_L + (V_0 - V_L)e^{-\frac{t}{\tau}}$



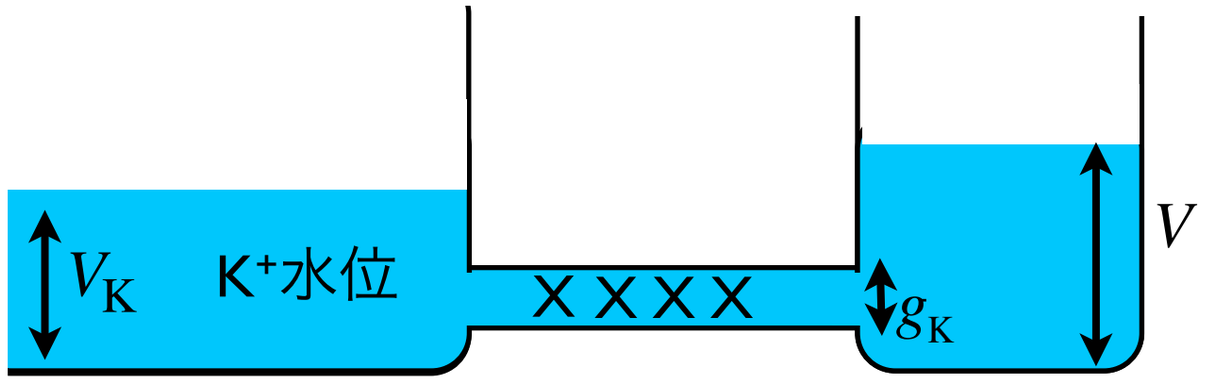
重要：　τは反応の遅れ時間を表している

K⁺チャネル電流　　$C\frac{dV}{dt} = I_L + I_K + I_{Na} + I_{ext}$

$$I_K = g_{\mathrm{K}} n^4 (V_{\mathrm{K}} - V)$$

n： 各ゲートが開いている確率

n^4：4つのゲート全てが開いている確率



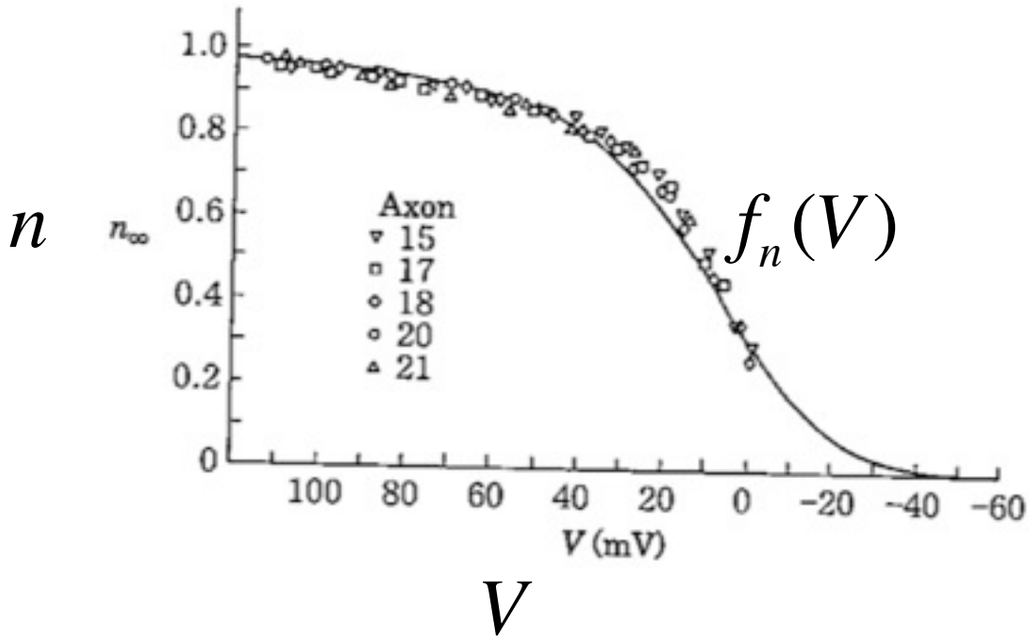
4つのゲート

ゲートが開く確率の従う微分方程式

実験計測からの知見：

膜電位よって、ゲートが開いている確率が決まっている。

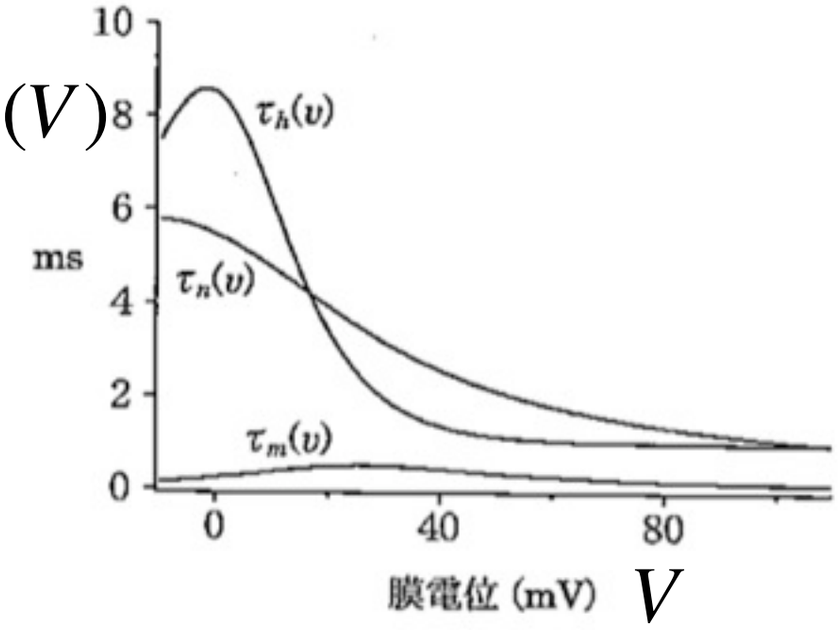
反応にかかる遅れ時間も膜電位に依存する。



n

$f_n(V)$

V



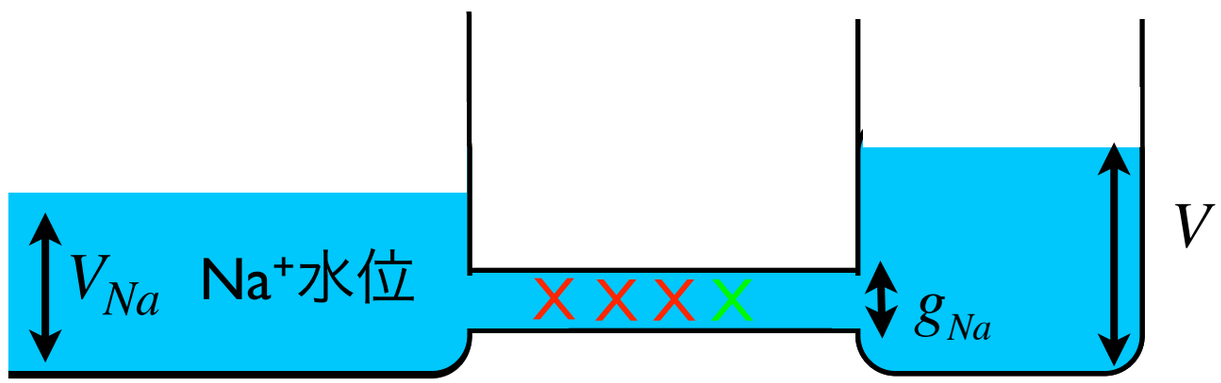
$\tau_n(V)$

V

$$\frac{dn}{dt} = \frac{f_n(V) - n}{\tau_n(V)}$$

Na^+チャネル電流

$$I_{Na} = g_{Na} m^3 h (V_{Na} - V)$$



m, h：各ゲートが開いている確率

$m^3 h$：4つのゲート全てが開いている確率

2種類の計4つのゲート

$$\frac{dm}{dt} = \frac{f_m(V) - m}{\tau_m(V)}$$

$$\frac{dh}{dt} = \frac{f_h(V) - h}{\tau_h(V)}$$

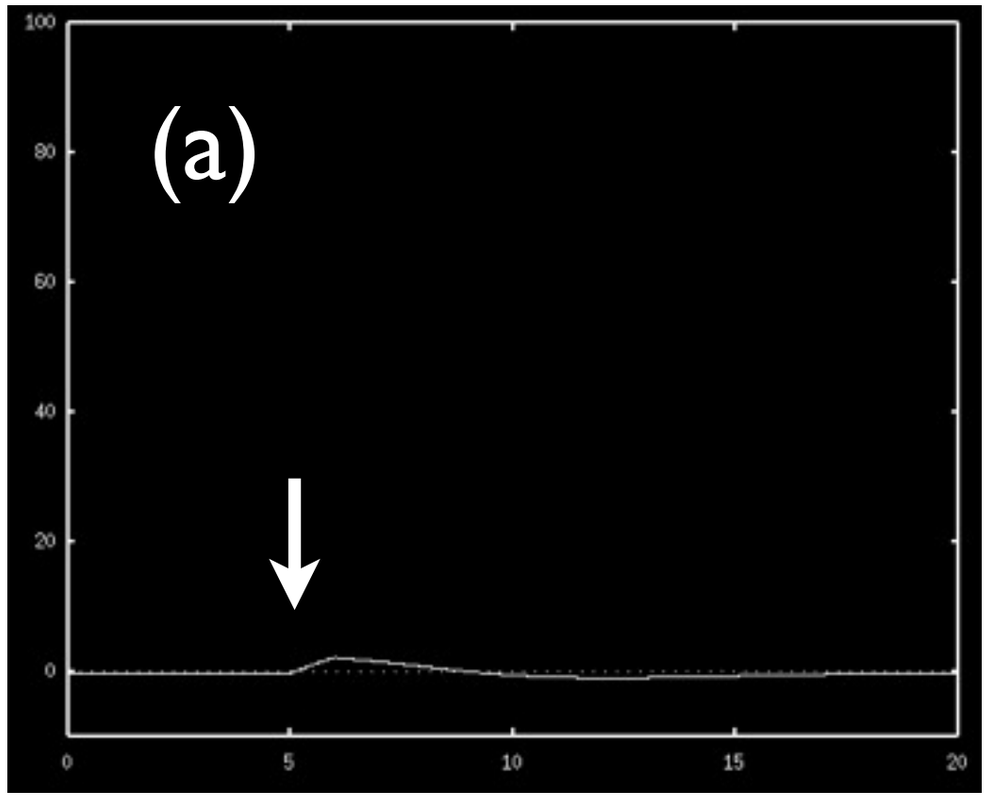
数値「実験」 $C\dfrac{dV}{dt} = \cdots + I_{ext}$

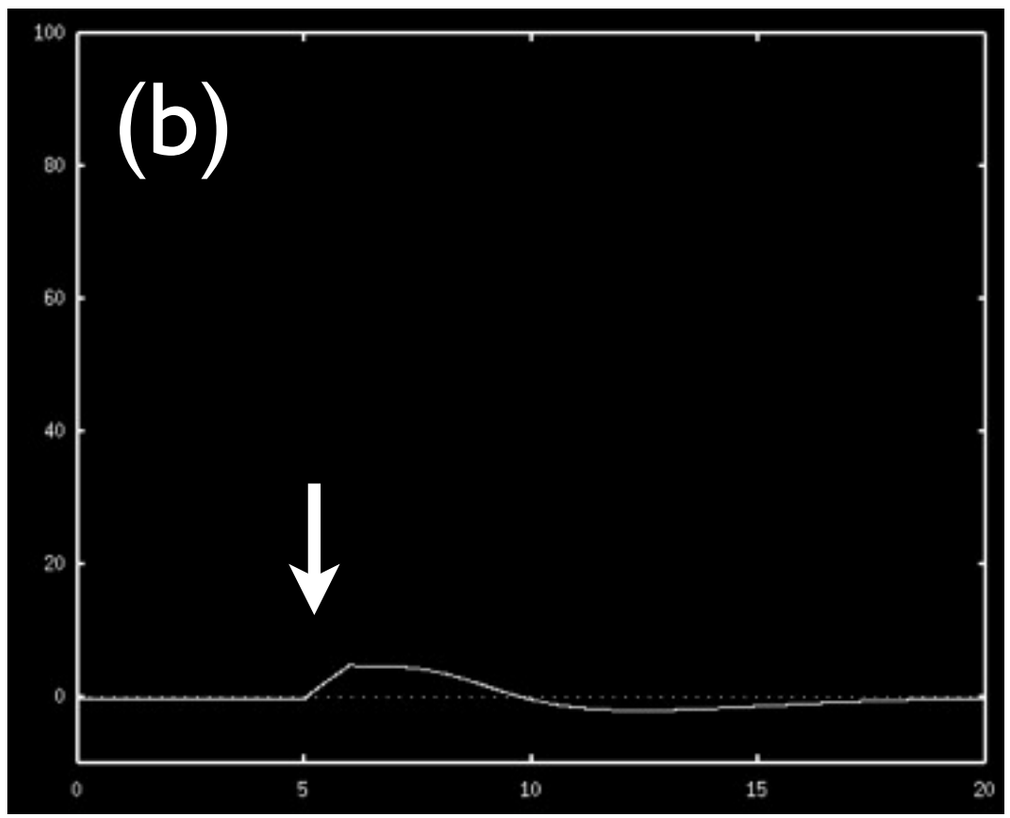
t=5から1msの間

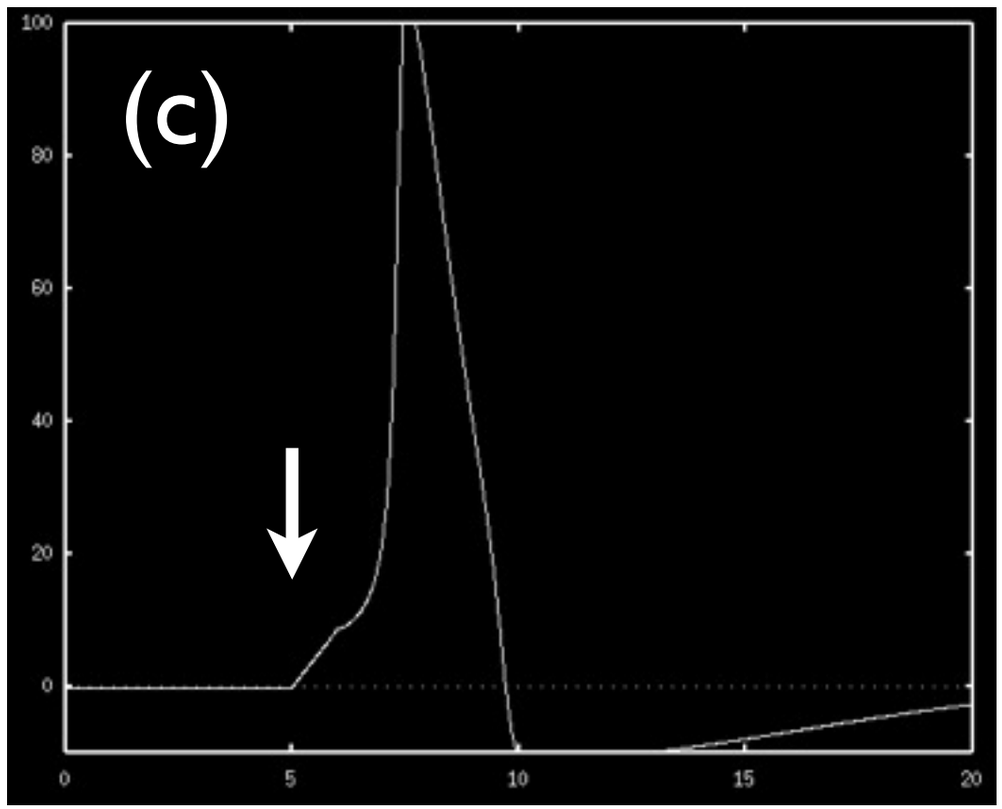
(a) $I_{ext} = 3\ [\mu \mathrm{A/cm}^2]$

(b) $I_{ext} = 6$

(c) $I_{ext} = 10$







Hodgkin-Huxley モデル

$$C\frac{dV}{dt} = I_L + I_K + I_{Na} + I_{ext}$$

$$\frac{dn}{dt} = \frac{f_n(V) - n}{\tau_n(V)}$$

$$\frac{dm}{dt} = \frac{f_m(V) - m}{\tau_m(V)}$$

$$\frac{dh}{dt} = \frac{f_h(V) - h}{\tau_h(V)}$$

$$I_L = g_L(V_L - V)$$

$$I_K = g_K n^4 (V_K - V)$$

$$I_{Na} = g_{Na} m^3 h (V_{Na} - V)$$

I_{ext} ：外部からの入力電流

$f_?, \tau_?$ ：実験観測結果を
よくフィットする関数

神経興奮を数理モデルで確かに再構築できた.

実験的に得られたK^+チャネル，Na^+チャネルの膜電位依存性が

（イカ軸索の）神経興奮の十分条件であることを示した.

しかし神経興奮のメカニズムはまだ

「言葉」になっていない.

FitzHugh-Nagumoモデル：

縮約によって神経興奮機構を「言葉」にする

アイディア

（A）タイムスケールの差を利用して１変数を消去

（B）2つの類似な変数を１つで記述

4次元から2次元へ縮約.

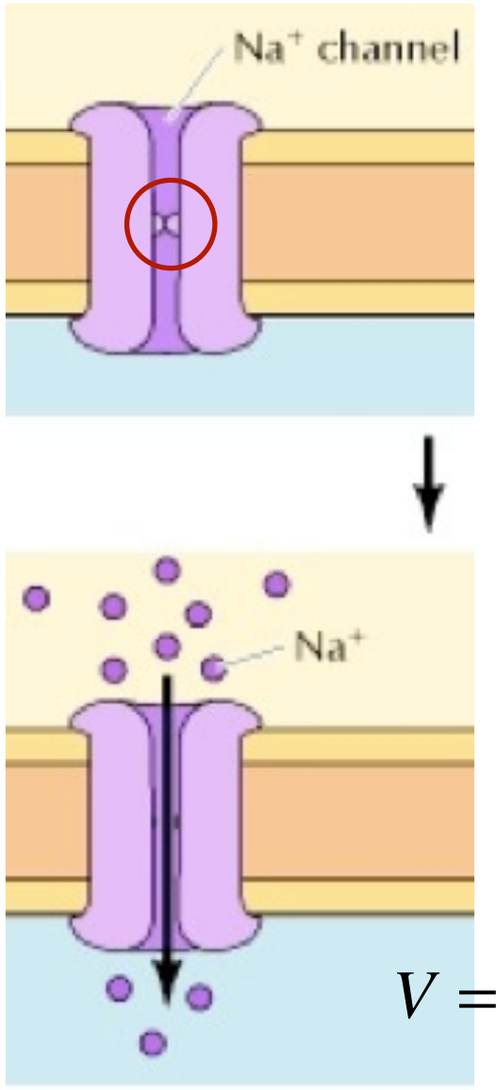
4次元空間はエタイがしれないが

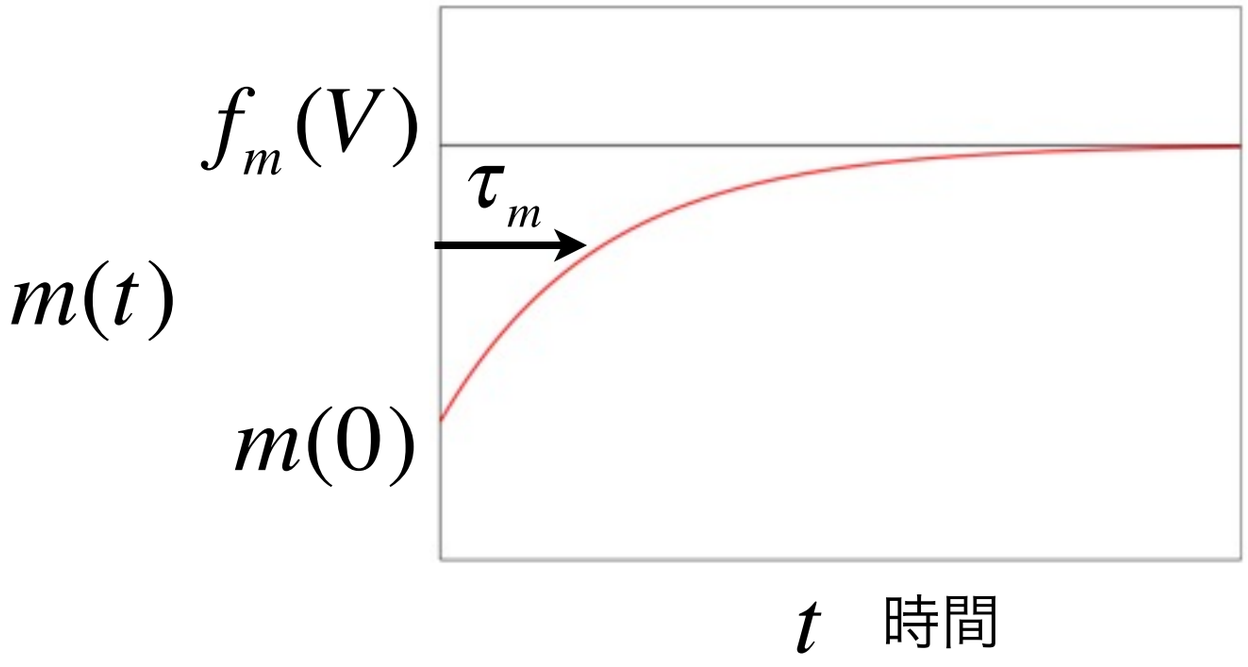
2次元ならヒトでも理解できる.

（A）Naチャネルのゲート変数

$$\frac{dm}{dt} = \frac{f_m(V) - m}{\tau_m(V)}$$

Vの時間変化を無視し、定数とする





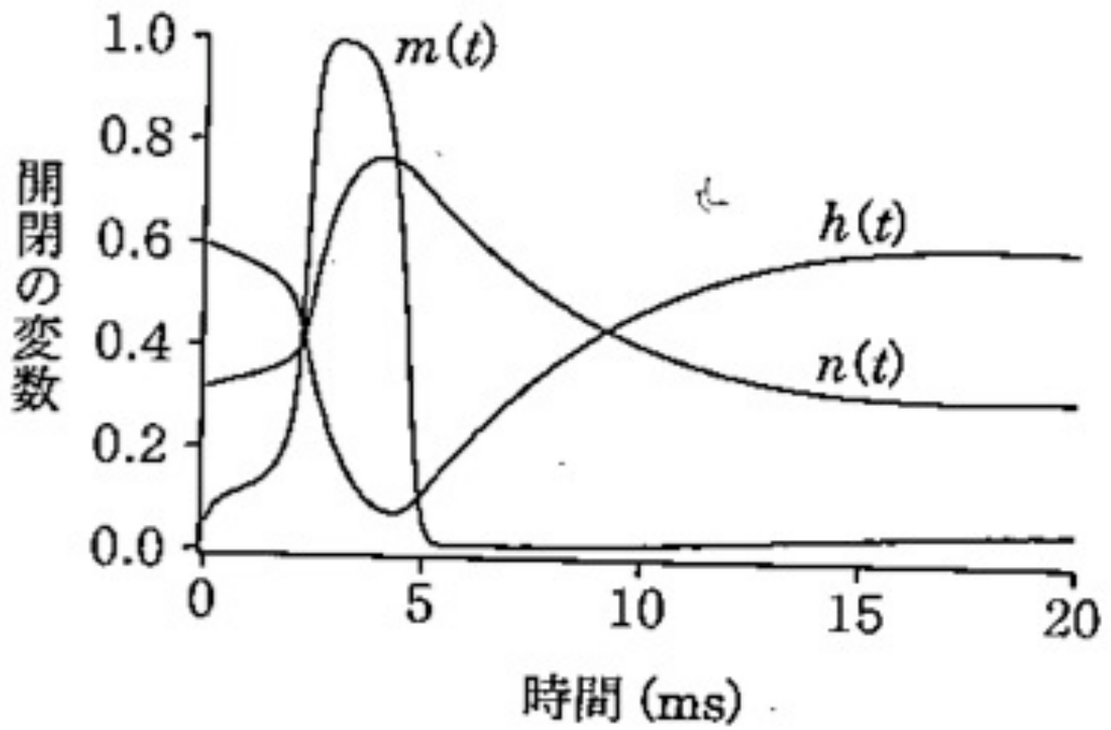
$$m(t) \to f_m(V)$$

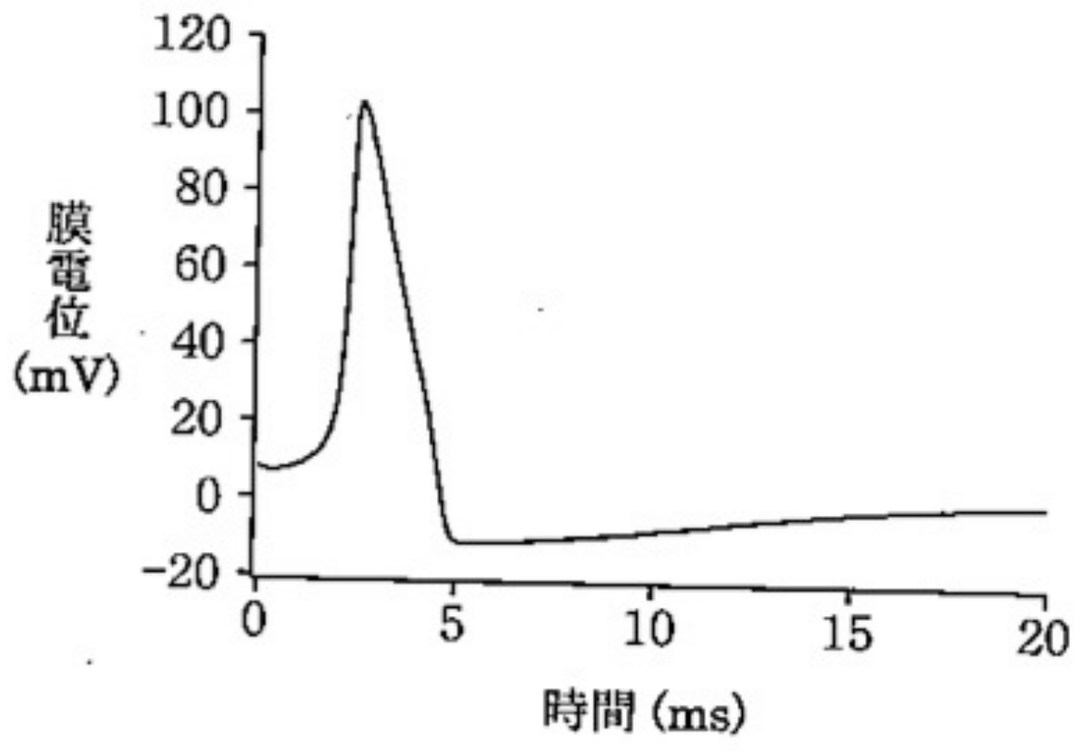
イカ軸索において、mは他の変数より反応が早い

$$m(t) \approx f_m(V)$$

「断熱消去」

（B）活動電位の波形をみる





nとhがそっくり！

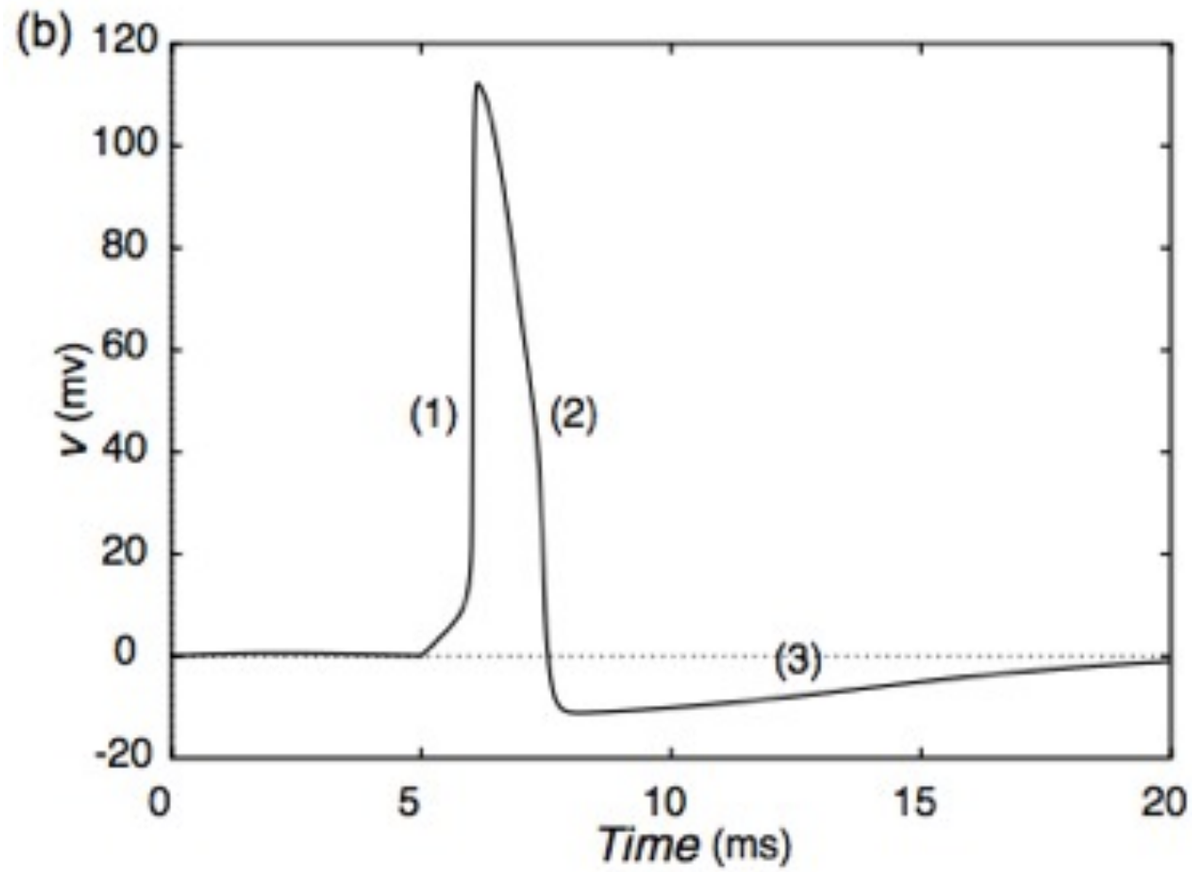
$$h(t) \approx 0.8 - n(t)$$

hの方程式はいらない

2変数版Hodgkin-Huxley モデル

$$C\frac{dV}{dt} = F_V(V,n) + I_{ext}$$

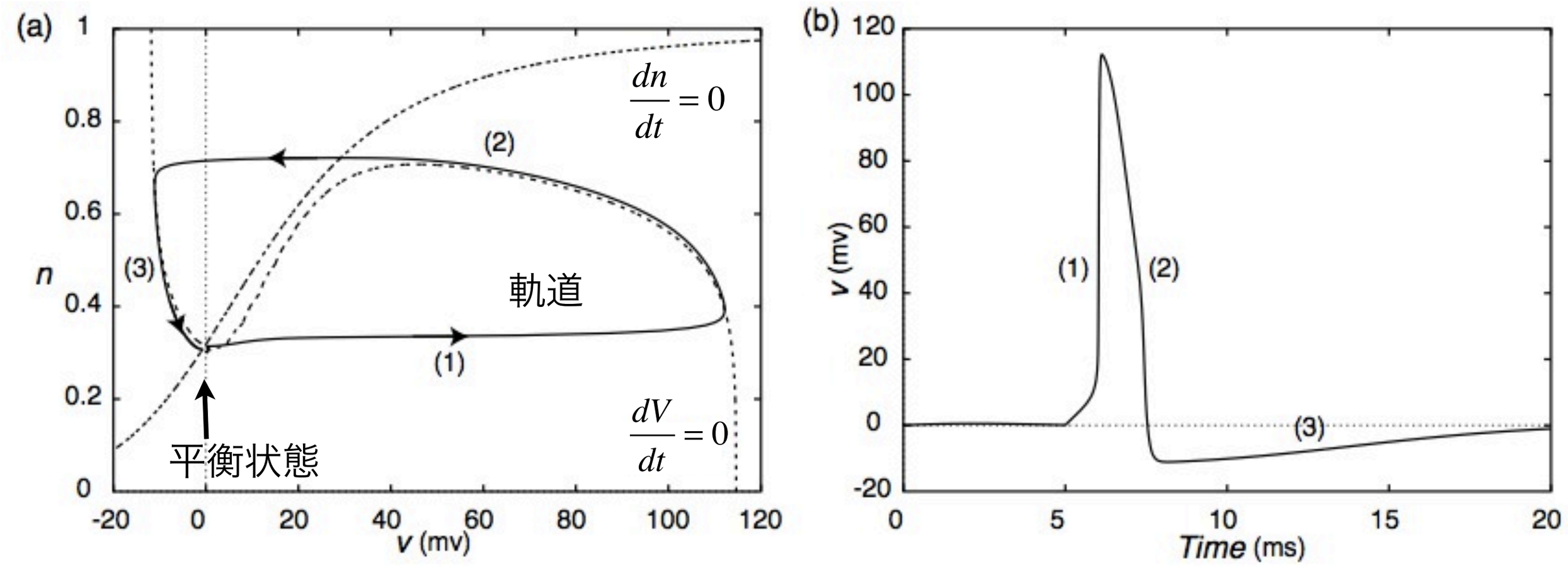
$$\frac{dn}{dt} = F_n(V,n)$$



（高松敦子さん（早稲田）の講義ノートより）

神経興奮の性質は定性的に保たれている

2次元だと興奮が絵でわかる



（高松敦子さん（早稲田）の講義ノートより）

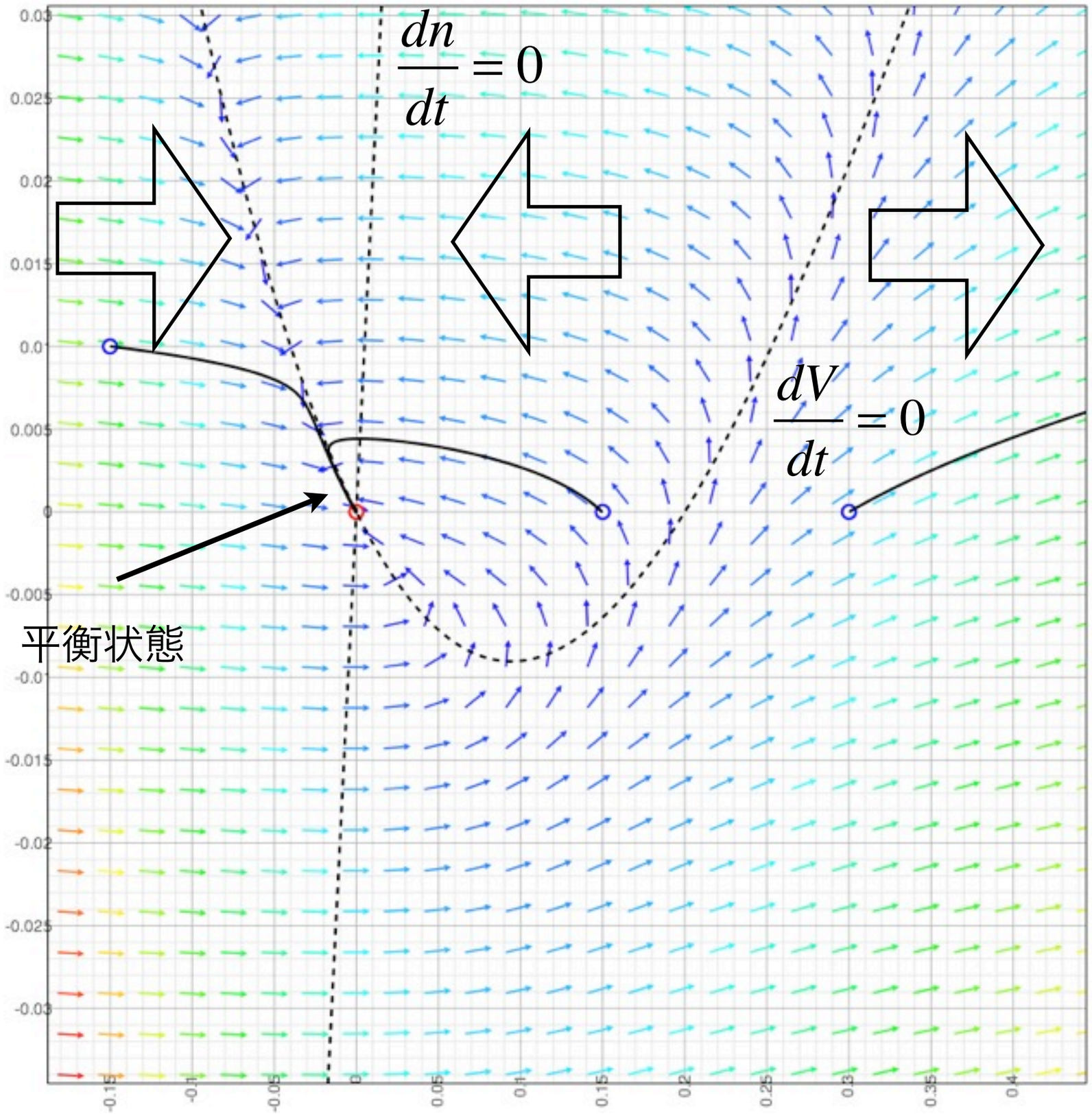
$$C\frac{dV}{dt}=F_V(V,n)=0$$

$$\frac{dn}{dt}=F_n(V,n)=0$$

この２つの曲線を「ヌルクライン」と呼ぶ.

運動方向を決める、非常に重要な曲線！

平衡状態近辺を拡大



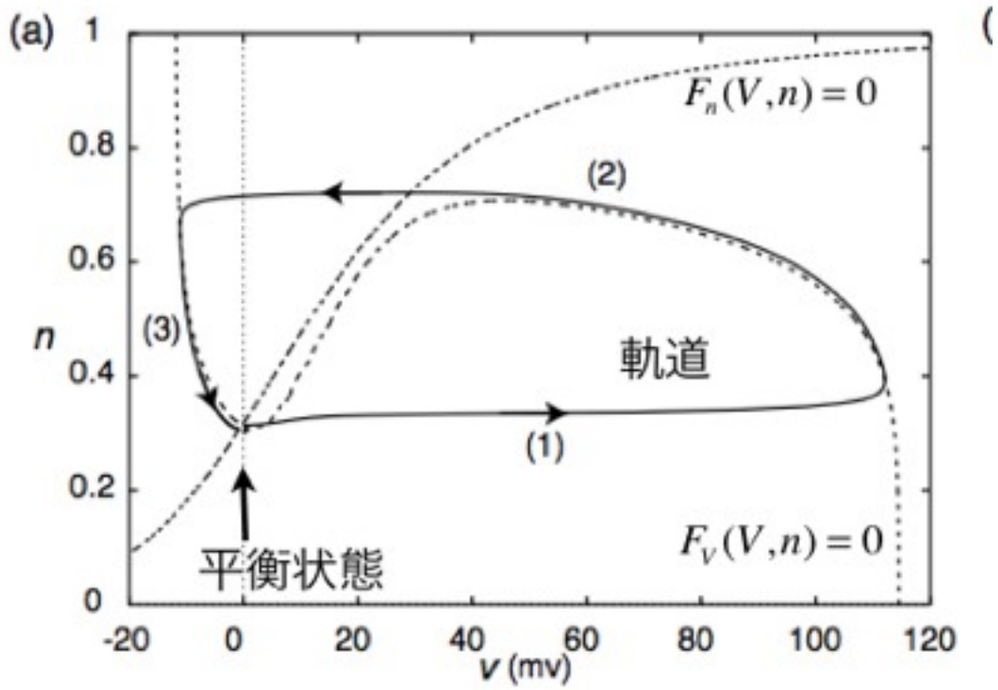
n

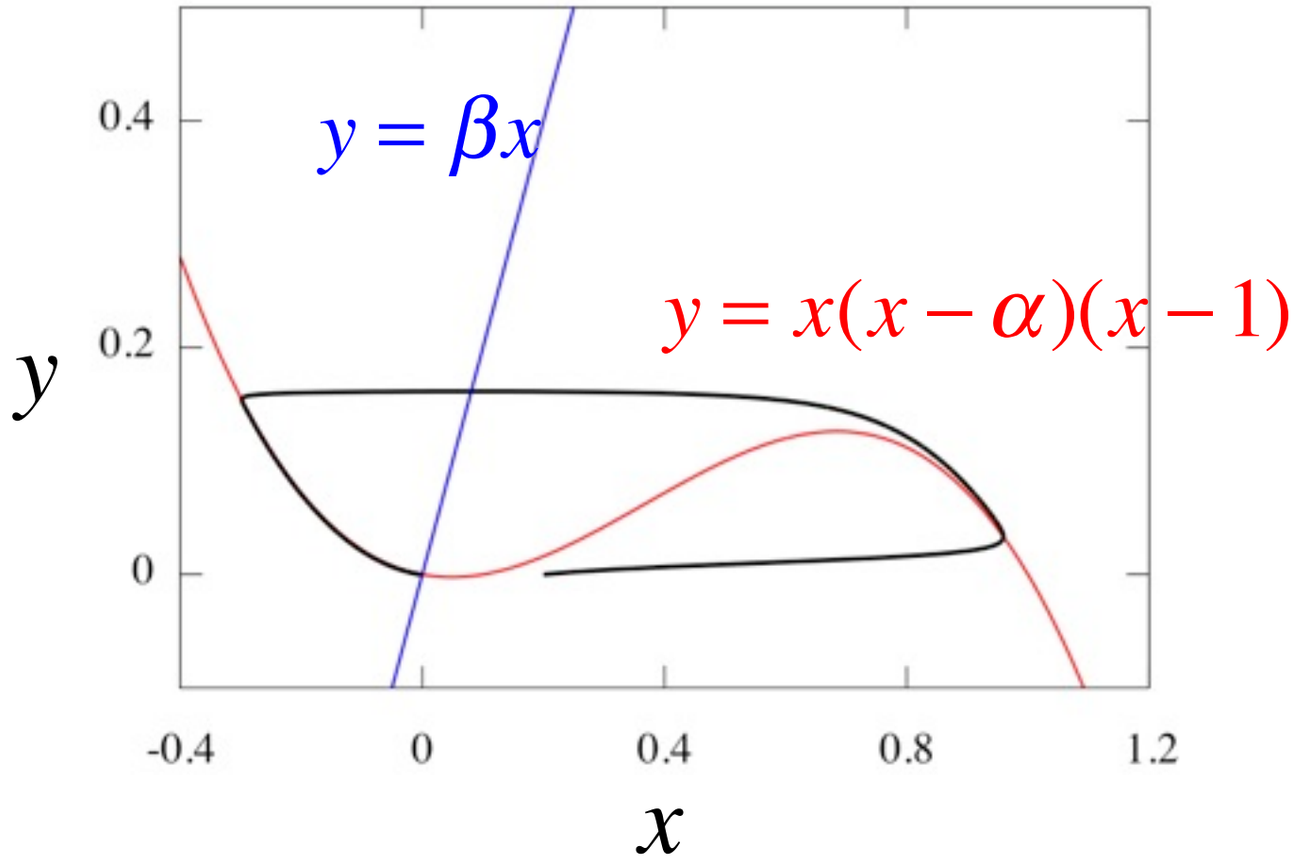
V

平衡状態

Vの変化する方向

ヌルクラインが似ていればいい





$$\frac{dx}{dt} = x(x-\alpha)(x-1) - y$$

$$\frac{dy}{dt} = \epsilon(\beta x - y)$$

FitzHugh-Nagumoモデル

神経興奮メカニズムの「言葉」：

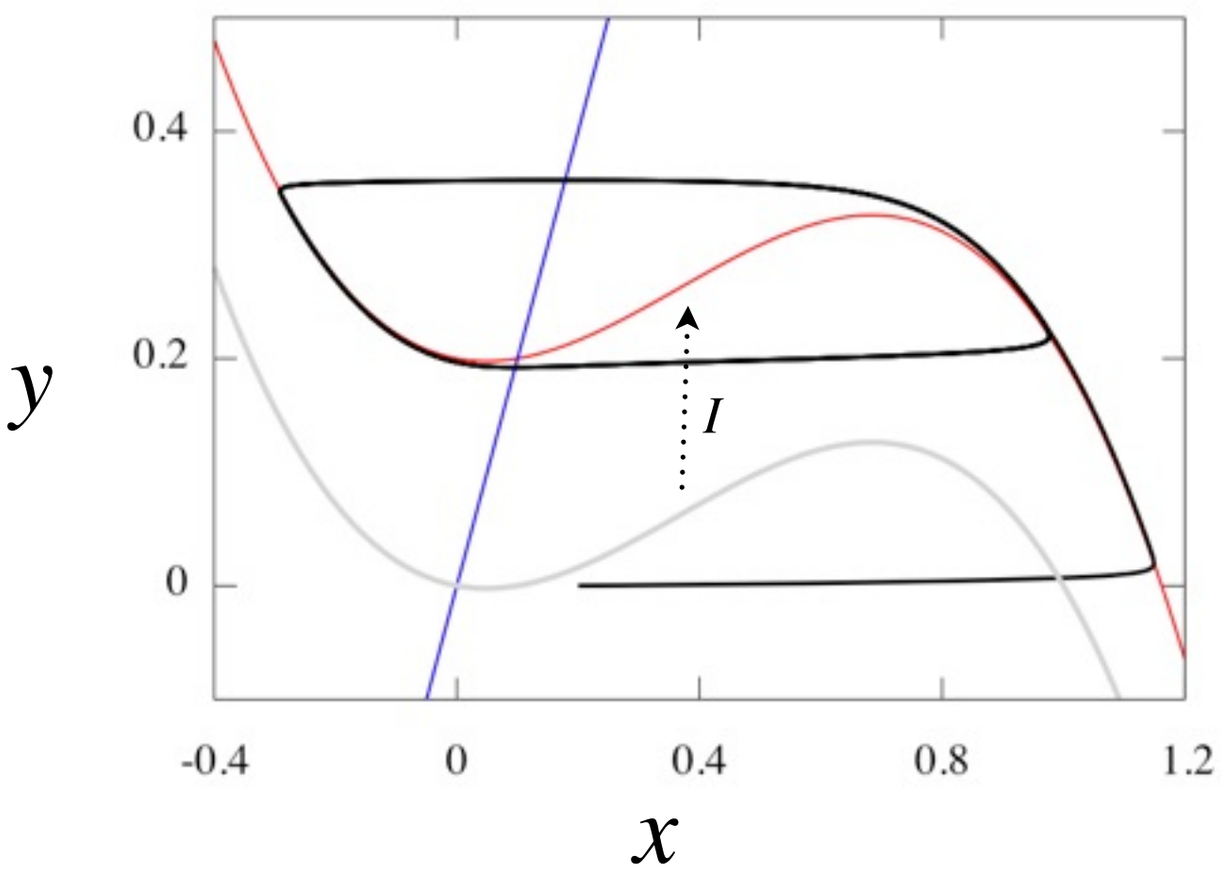
ヌルクラインの構造と時間スケールの差

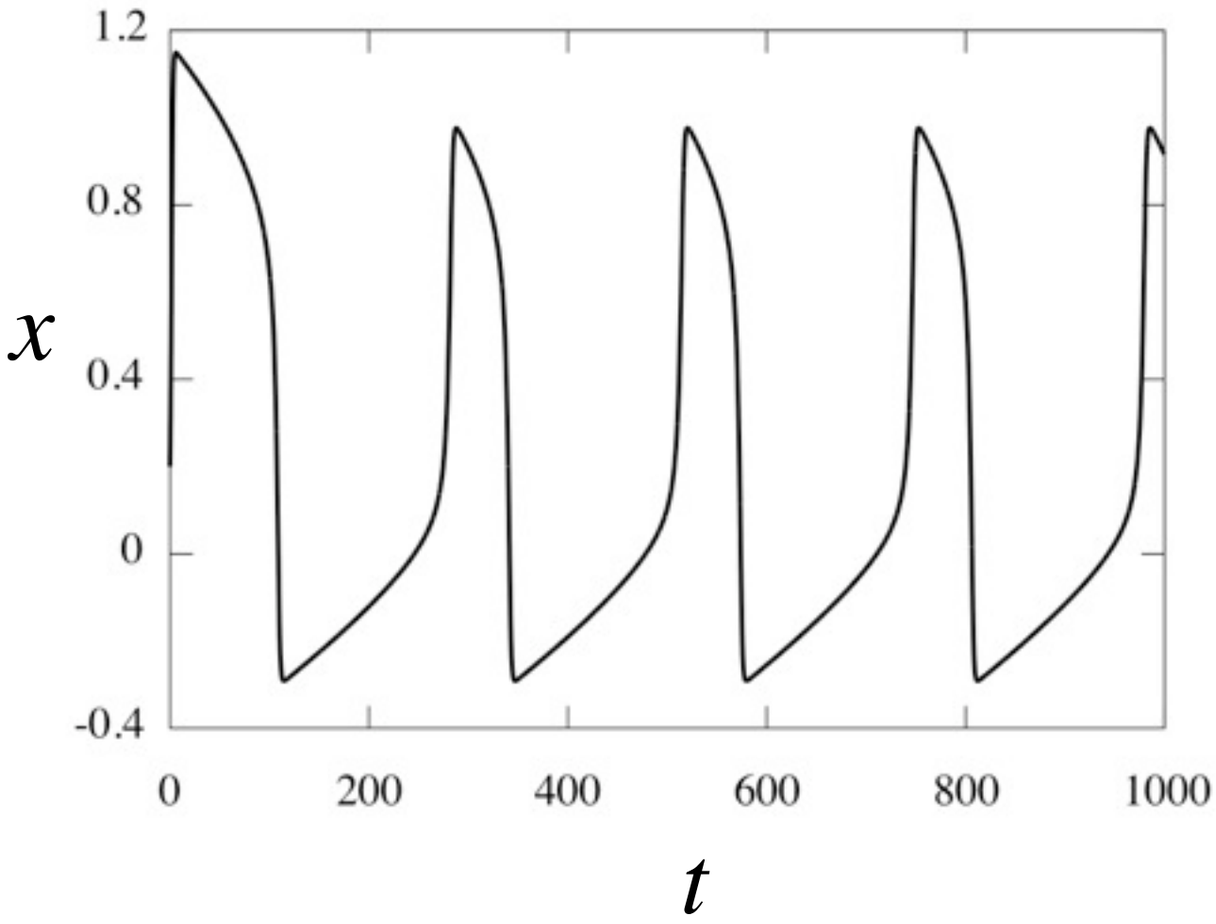
振動もわかりやすく理解できる

$$\frac{dx}{dt} = x(x-\alpha)(x-1) - y + I$$

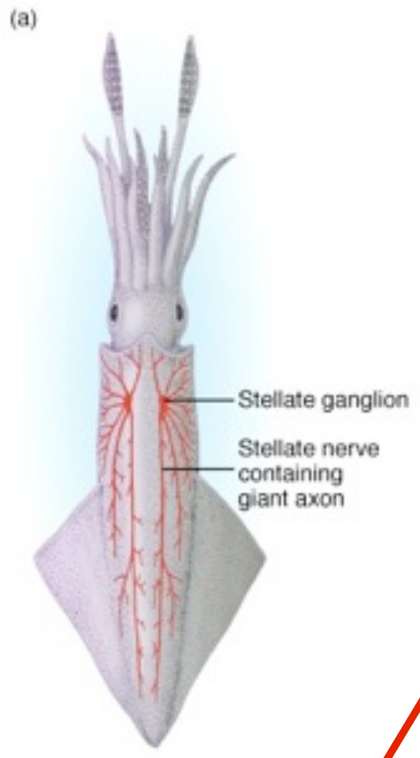
$$\frac{dy}{dt} = \epsilon(\beta x - y)$$

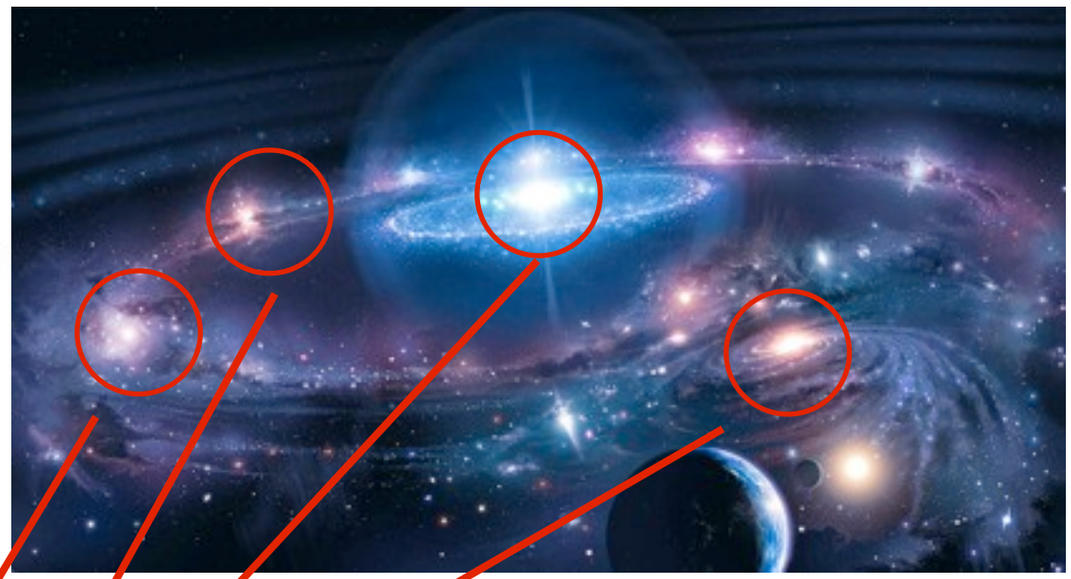
Iを大きくすると３次関数が
上に移動して...





イカ





ここまでの
まとめ

Hodgkin-Huxley
（４次元）

テクノロジー（計算機）が
あれば理解可能

「縮約」

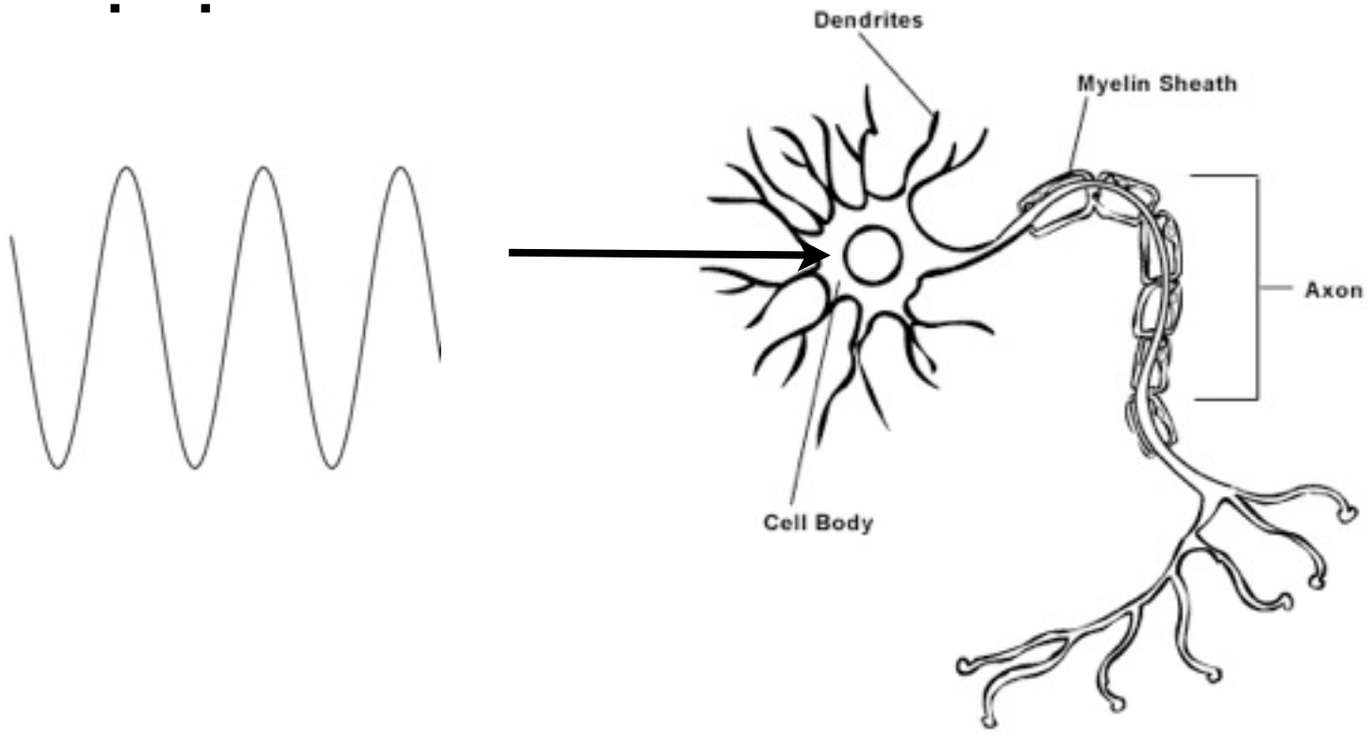
FitzHugh-Nagumo
（2次元）

我々の言葉の世界へ

縮約の道はつづく

神経細胞＋定常電流＝振動

振動＋変動電流＝？？

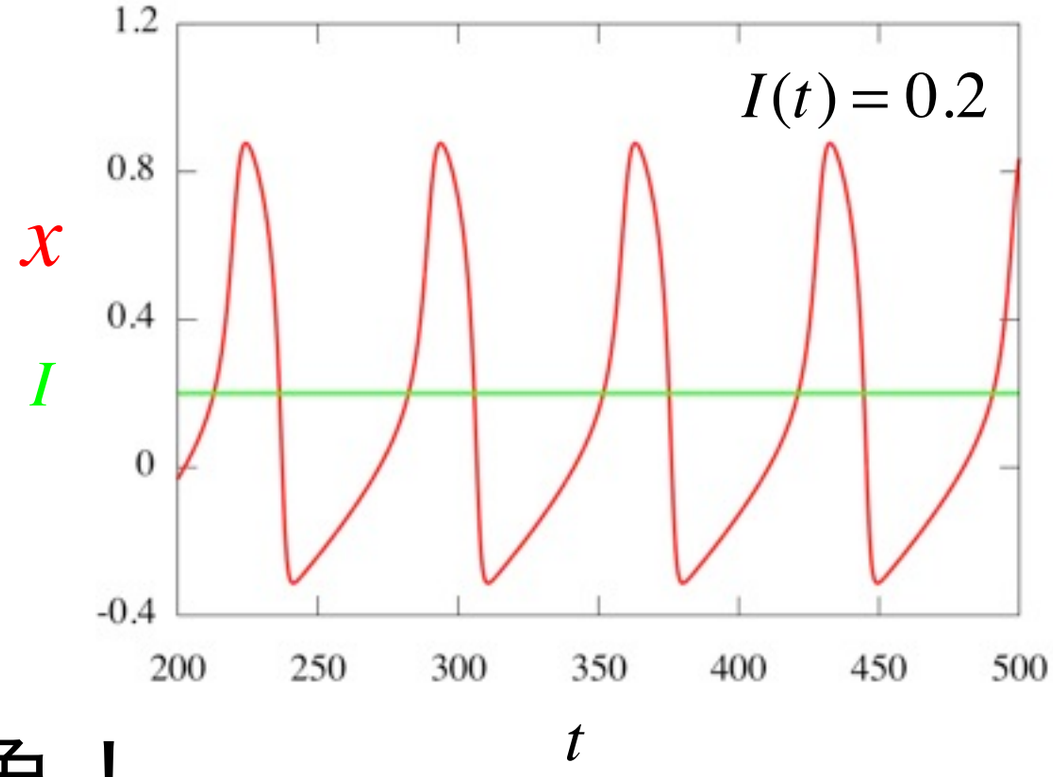


FitzHugh-Nagumoでも「言葉」にできない

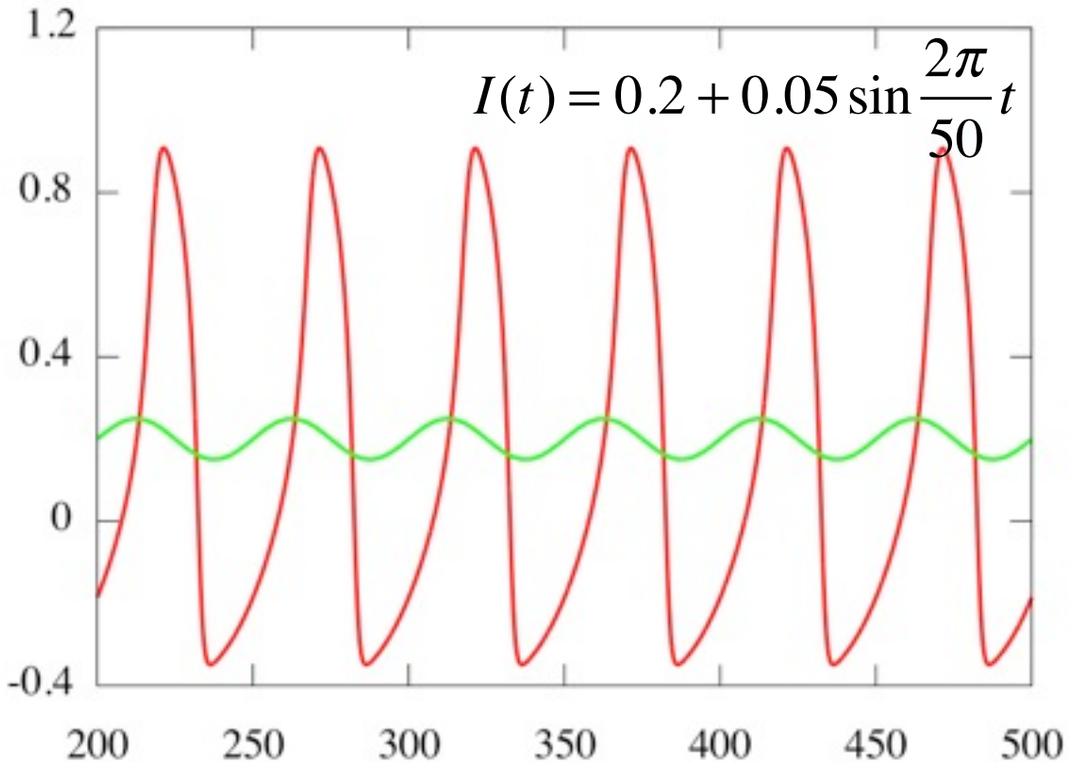
FHNで数値実験

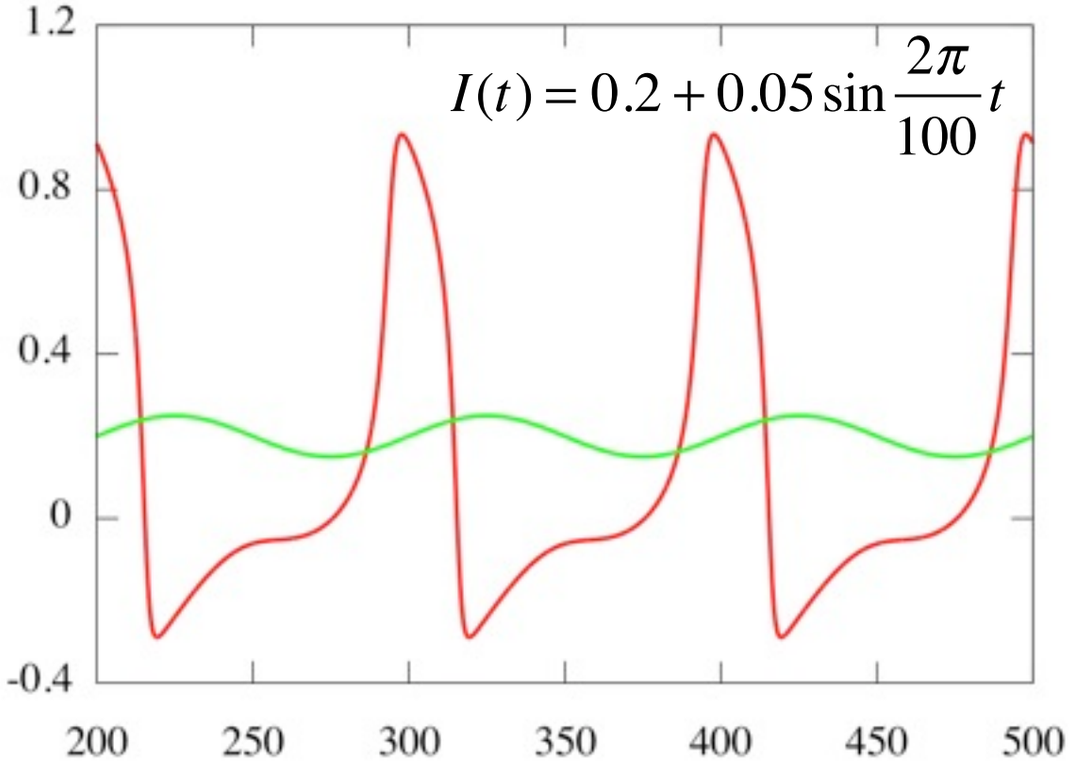
$$\frac{dx}{dt} = f_x(x,y) + I(t)$$

$$\frac{dy}{dt} = f_y(x,y)$$



同期現象！



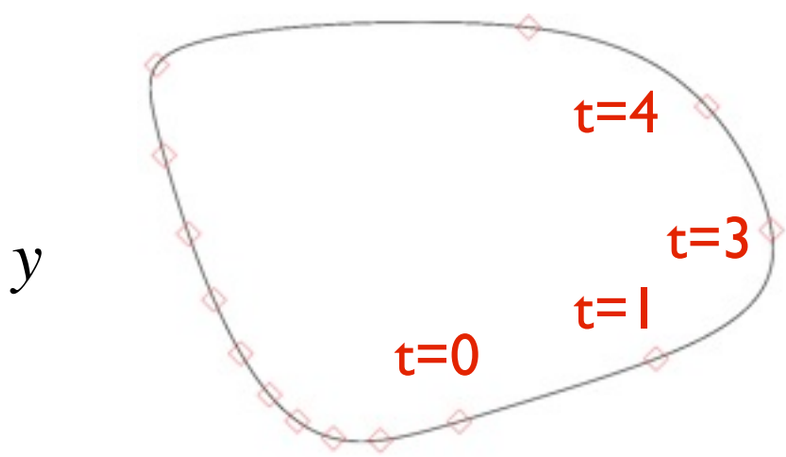


さらなる縮約：位相モデル

$$\frac{dx}{dt} = f_x(x,y) + I_0 + Kp(t)$$

$$\frac{dy}{dt} = f_y(x,y)$$

振動子の固有の軌道 $K = 0$



手順１：振動子の軌道に対して位相を定義

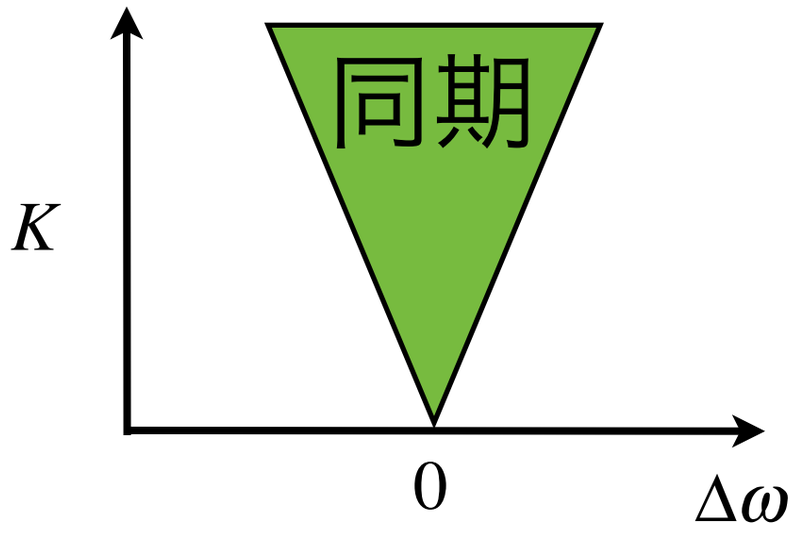
$$\frac{d\phi}{dt} = \omega \qquad \text{つまり} \qquad \phi = \omega t \ (0 \le \phi \le 2\pi)$$

手順２：座標変換＋線形近似

$$\frac{d\phi}{dt} = \omega + KZ(\phi)p(t)$$

$Z(\phi)$：(無限小)位相応答関数

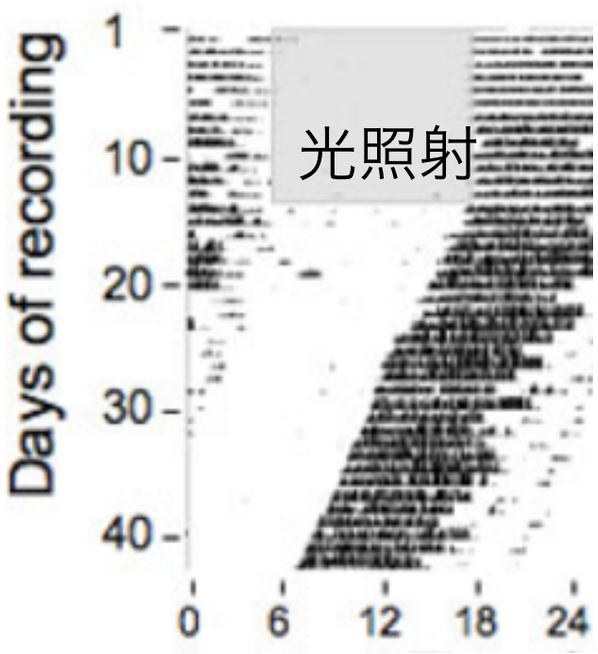
(Phase response curve)



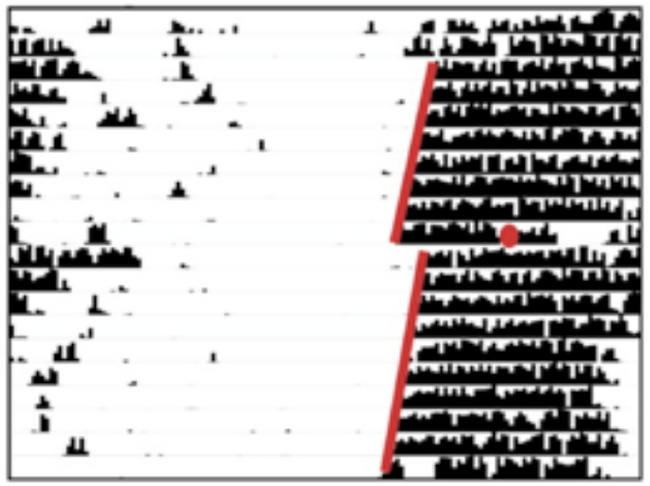
どんな振動子でも同様。同期が「普通」であることがわかる

位相応答関数は概日リズムでおなじみ

暗室中



時刻 t



●：光照射　→時計がずれる

モデルがなくても位相モデルが作れる！！

$$\frac{d\phi}{dt} = \omega + Z(\phi)p(t)$$

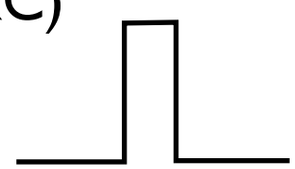
t :　外界の時刻

$\phi(t)$:　個体の「体内時刻」

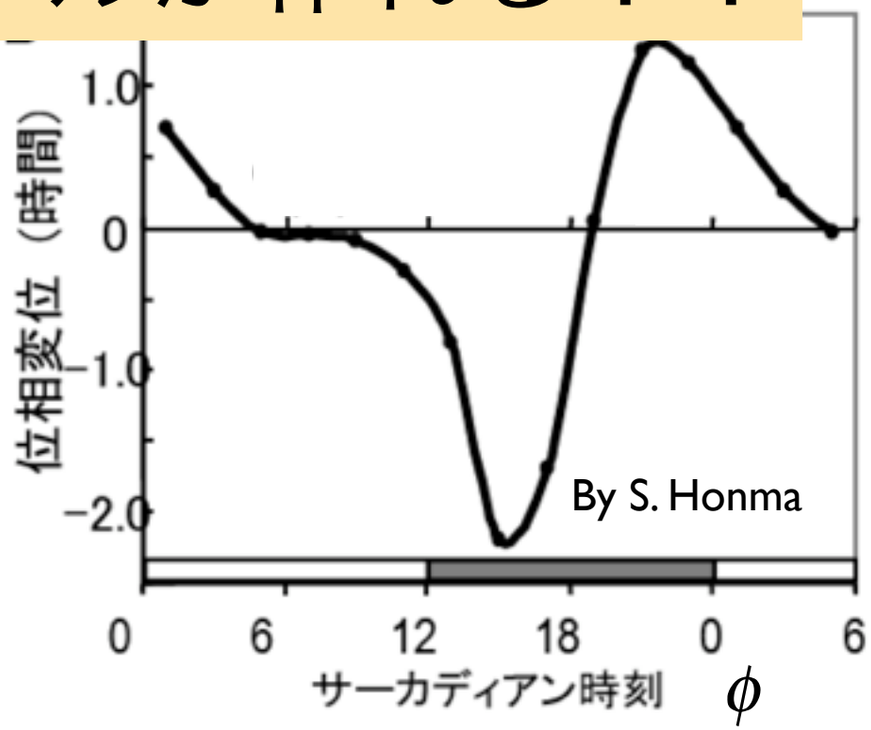
ω :　自然振動数　$2\pi / 23.5$

$Z(\phi)$:　位相応答関数(PRC)

$p(t)$:　光の強度関数



$Z(\phi)$



（光を照射するタイミング）

おまけ（本質？）

縮約したモデルで遊ぼう

蔵本モデル

$$\frac{d\phi_i}{dt} = \omega_i + K\sum_{i=1}^{N}\sin(\phi_j - \phi_i)$$

・N個の振動子

・ばらばらの固有振動数

→位相はばらばらになる

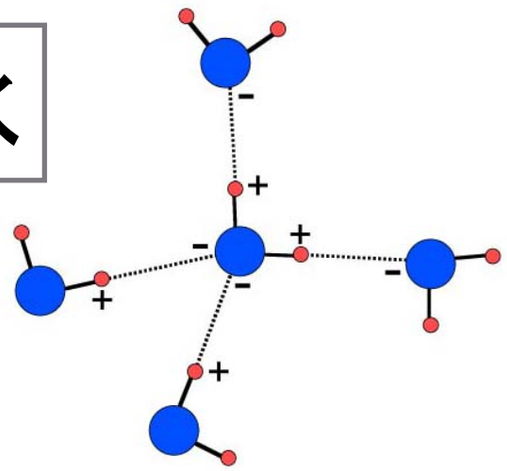
・全部が全部と相互作用。

→位相をそろえたがる

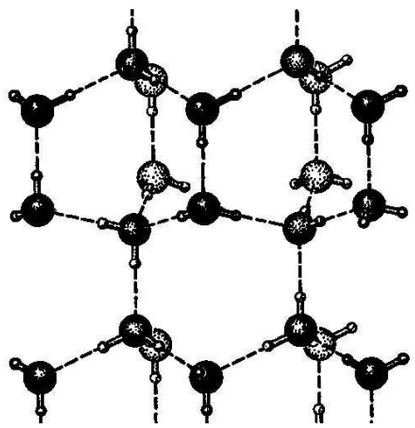
相転移としての同期現象

もともとバラバラなのものが、コミュニケーションにより秩序を持つ

水

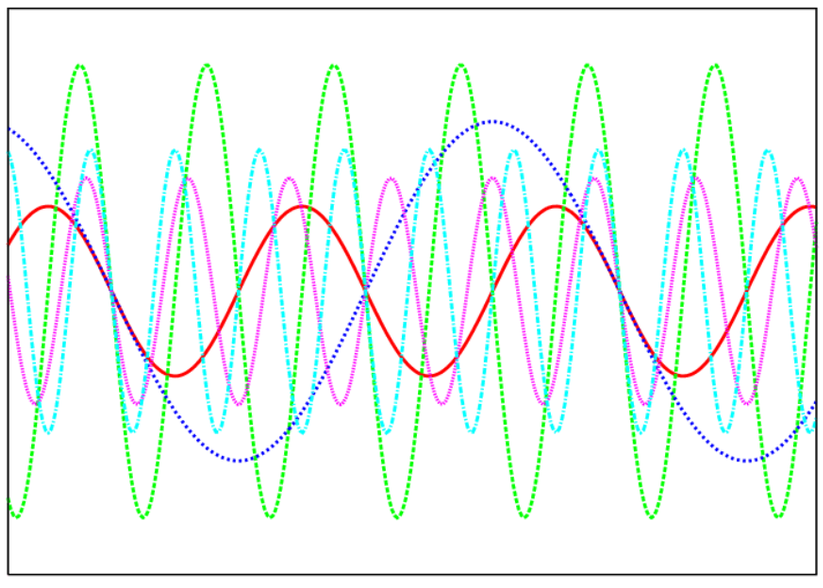


相転移

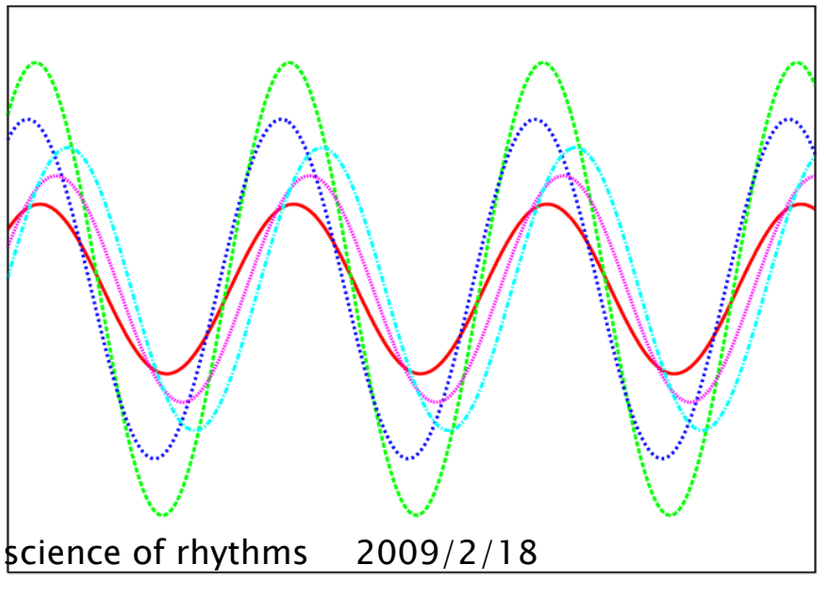


氷

バラバラになる傾向　<　コミュニケーションの力



蔵本転移



位相モデルを使うと、振動子集団ネットワークのような、超複雑なものも解ける場合がある。

すると「言葉」になる

神経興奮の縮約のまとめ

	変数の数	現象の豊かさ	数式から得られるメッセージ	遊び度
イカ	イカ	イカ	イカ	イカ
HHモデル	4	振動 興奮 カオス	計算機 必須	神経細胞
FHNモデル	2	振動 興奮	図形的に 理解可能	心筋細胞 化学反応 ・・・
位相モデル	1	振動	解けることあり	体内時計 ホタル 「振動子」

メッセージ１：理論の位置づけ

モデル化はすでに劇的な縮約（イカ→HH）。
その後も解析（理解）のためにいろんな近似を使ってる。

その根本的な思想は
「この近似では、定性的な性質が保たれているであろう。」

Math is the lie that makes us realize the truth.

S. Strogatzが＊＊＊からパクッた言葉

http://opinionator.blogs.nytimes.com/2009/05/19/math-and-the-city/

メッセージ２：理論家と実験家の幸せな関係

・実験家が、数式を操れる必要はあまりない。

（数値解析はできると便利だとは思うが。）

縮約などの近似や解くことは、理論家にやらせておけばいい。

でも、数式の意味、数式の示していることは、実験家もわかる。

そうして「理論的な考え方」ができるようになれば

違う発想方法を手に入れることができる。

「新しい道具」としての理論

「新しい道具」としての理論家

それで実験生物学者は何をするべき？

理論家の精神を知るには

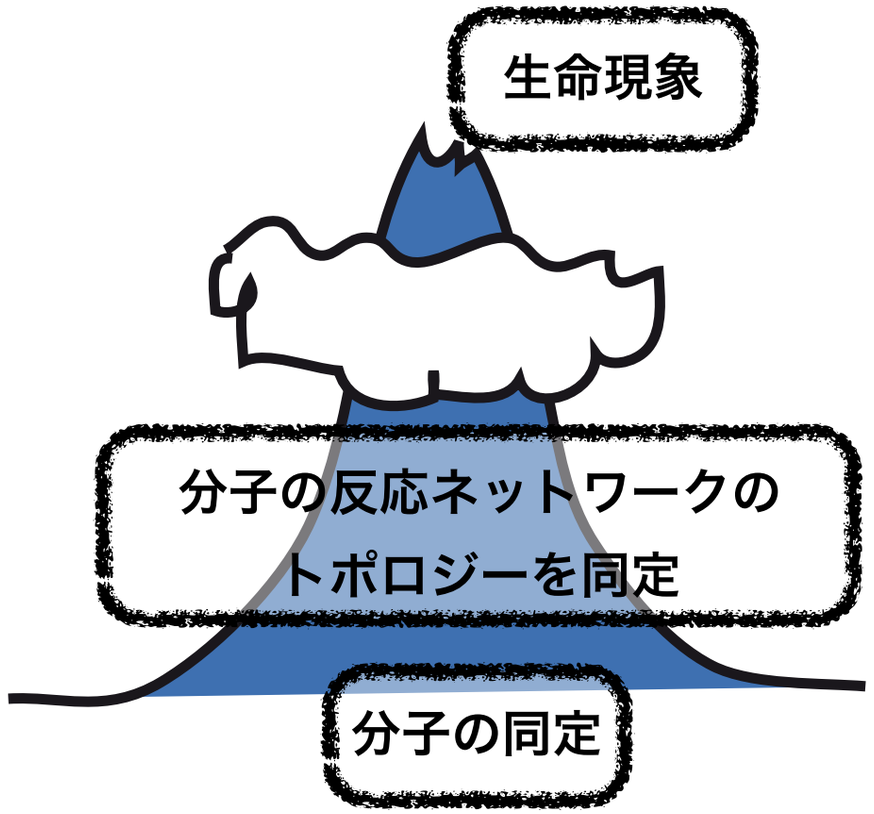
- 理論家の話すやさしい話をきいてみる(でもあんまりチャンスがない！)
- 自分の好きな理論家の論文を読んでみる
- やさしい教科書を読む
- 理論家の集まりそうな研究会に潜入する(メーリングリスト:complexに入る)
- 飲みに行く

運良く理論家と話せるチャンスがあったら

- 理論家には縮約の精神があることを前提で話す
(生物学者が実験結果をできるだけ生のままとり扱うのとは逆の精神)

- 実験結果を再現するモデルを作って！と頼むのは....
- 理論家と一緒に問題を作ると良いかも

雲を取り払ってくれるのが
理論家の仕事？



郡さんの論文を読んでみる

Entrainment of Randomly Coupled Oscillator Networks by a Pacemaker

Hiroshi Kori[1,2,*] and Alexander S. Mikhailov[2]

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Entrainment of Randomly Coupled Oscillator Networks by a Pacemaker

Hiroshi Kori[1,2,*] and Alexander S. Mikhailov[2]

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(Received 20 February 2004; published 15 December 2004)

Entrainment by a pacemaker, representing an element with a higher frequency, is numerically investigated for several classes of random networks which consist of identical phase oscillators. We find that the entrainment frequency window of a network decreases exponentially with its depth, defined as the mean forward distance of the elements from the pacemaker. Effectively, only shallow networks can thus exhibit frequency locking to the pacemaker. The exponential dependence is also derived analytically as an approximation for large random asymmetric networks.

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アブスト

Pacemakers are wave sources in distributed oscillatory systems typically associated with a local group of elements having a higher oscillation frequency. Target patterns, generated by pacemakers, were the first complex wave patterns observed in the Belousov-Zhabotinsky system [1]. Pacemakers play an important role in the functioning of the heart [2] and in the collective behavior of *Dictyostelium discoideum* [3]. They are also observed in large-scale ecosystems [4]. In addition to pacemakers produced by local heterogeneities in the medium [5], self-organized pacemakers in uniform birhythmic media have been theoretically studied [6]. While the majority of related investigations have so far been performed for systems with local diffusive coupling between the elements, pacemakers can also operate in oscillator networks with complex connection topologies. The circadian rhythm in mammals is a daily variation of 24 h that regulates basic physiological processes in such animals [7]. It is produced by a complex network of neurons forming the so-called suprachiasmatic nucleus (SCN) [8]. As recently shown, this oscillator network undergoes spontaneous synchronization in the absence of any environmental input, but its intrinsic synchronization period is then significantly longer than 24 h [9]. Therefore, the actual shorter rhythm results from the environmental entrainment and must be externally imposed. The entrainment is mediated by direct photic inputs from eyes into the SCN, which undergo periodic daily variation. However, it is known that only a distinct subset of neurons in this network is directly influenced by photic inputs [10]. Hence, functioning of this particular neural system is crucially dependent on the ability of the entire complex network to become entrained by an external pacemaker. Analogous behavior can also be expected, for example, in heterogeneous arrays of globally coupled electrochemical oscillators where synchronization and entrainment have been experimentally demonstrated [11].

イントロ

To understand the operation of pacemakers in networks with complex connection topologies, the action of a pacemaker in a random oscillator network should first be investigated. In this Letter, networks of identical phase oscillators with random connections are considered. A pacemaker is introduced as a special element whose oscillations have a higher frequency and are not influenced by the rest of the system. Depending on the pacemaker frequency and the strength of coupling, the pacemaker can entrain the entire network, so that the frequencies of all its elements become equal to that of the pacemaker. We find that the entrainment window decreases exponentially with the depth of a network, defined as the mean forward distance of its elements from a pacemaker, and thus only shallow networks can effectively be entrained. This result is confirmed in numerical simulations for several different classes of random networks, including small-world graphs. It is further analytically derived as an approximation for random networks with asymmetric connections.

Model

We consider a system of $N + 1$ phase oscillators, one of them being a pacemaker. The model is given by a set of evolution equations [12] for the oscillator phases ϕ_i and the pacemaker phase ϕ_0,

$$\dot{\phi}_i = \omega - \frac{\kappa}{pN}\sum_{j=1}^{N} A_{ij}\sin(\phi_i - \phi_j) - \mu B_i \sin(\phi_i - \phi_0),$$

$$\dot{\phi}_0 = \omega + \Delta\omega.$$

The topology of network connections is determined by the adjacency matrix $\mathbf{A}$ whose elements A_{ij} are either 1 or 0. The element with $i = 0$ is special and represents a pacemaker. Its frequency is increased by $\Delta\omega$ with respect to the frequency ω of all other oscillators [13]. The pacemaker is acting on a randomly chosen subset of N_1 elements, specified by B_i taking values 1 or 0. The total number of connections to the pacemaker, $N_1 = \sum_i B_i$, is fixed. The coupling between elements inside the network is characterized by strength κ. The strength of coupling from the pacemaker to the network elements is determined by the parameter μ. In absence of a pacemaker, such networks undergo autonomous phase synchronization at the natural frequency ω. Without loss of generality, we put $\omega = 0$. Moreover, we rescale time as $t' = t\Delta\omega$ and introduce rescaled coupling strengths $\kappa' = \kappa/\Delta\omega$ and $\mu' = \mu/\Delta\omega$. After such rescaling, the model takes the form of Eq. (1) with $\Delta\omega = 1$ and $\omega = 0$ (we drop primes in the notations for the rescaled couplings). In terms of the original model (1), increasing the rescaled coupling between the elements is equivalent either to an increase of coupling κ or to a decrease of the relative pacemaker frequency $\Delta\omega$.

The presence of a pacemaker imposes hierarchical organization. For any node i, its distance h with respect to the pacemaker is given by the length of the minimum forward path separating this node from the pacemaker. All N_1 elements in the group directly connected to the pacemaker have distances $h = 1$, the next elements that are connected to the elements from this group have distances $h = 2$, etc. Thus, the whole network is divided into a set of shells [14], each characterized by a certain forward distance h from the pacemaker. The set of numbers N_h is an important property of a network. The depth L of a given network, which is the mean distance from the pacemaker to the entire network, is introduced as $L = (1/N)\sum_h hN_h$. It should be noticed that such an ordering of network nodes is based solely on the forward connections descending down the hierarchy and does not depend on the distribution of reverse (upward) connections in the system.

First, we investigated *standard random asymmetric networks*, where independently for all connections $A_{ij} = 1$ with probability p and $A_{ij} = 0$ otherwise. Only sparse random networks with relatively low mean connectivity p and a small number N_1 of elements directly connected to the pacemaker were considered. Numerical simulations were performed for the networks of size $N = 100$ starting with random initial conditions for the phases of all oscillators. For each oscillator, its effective long-time frequency ω_i was computed as $\omega_i = T^{-1}[\phi_i(t_0 + T) - \phi_i(t_0)]$ with sufficiently large T and t_0. The simulations show that the response of a network to the introduction of a pacemaker depends on the strength κ of coupling between the oscillators. When this coupling is sufficiently large (and coupling μ to the pacemaker is also sufficiently strong as assumed below), the pacemaker entrains the whole network (i.e., $\omega_i = 1$ for all elements i). The frozen relative phases $\psi_i \equiv \phi_i - \phi_0$ are displayed in Fig. 1. Here, the elements are sorted according to their hierarchical shells. Despite random variations, there is a clear correlation between phases of oscillators and their positions in the hierarchy. Generally, the phase decreases for deeper shells, and the phase difference between the neighboring shells rapidly becomes smaller as deeper shells are considered. As the coupling strength κ is decreased, the entrainment breaks down at a certain threshold value κ_{cr}. Our simulations show that synchronization between the first and the second shells was almost always the first to break down, and the frequencies of the second and deeper shells remained equal in most cases for the considered random networks.

Figure 2 displays in the logarithmic scale the thresholds κ_{cr} for a large set of networks with different depths and

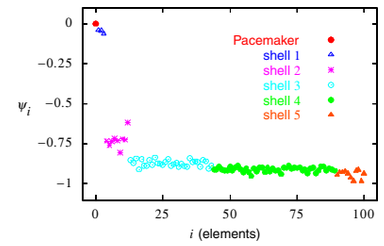

FIG. 1 (color online). Phases of elements in the entrained state: $N = 100$, $p = 0.05$, $N_1 = 3$, $\kappa = 100$, and $\mu = 1000$.

数値計算の方法

different numbers of elements in the first shell. Each group with a certain N_1 is displayed by using its own symbol. Every such group generates a cluster of data points. Correlation between the entrainment threshold and the network depth is apparent. The distributions inside each cluster and the accumulation of the clusters yield the dependence $\kappa_{cr}(L)$ of the entrainment threshold on the network depth. Note that the statistical variation of the data becomes larger for deeper networks with larger L and for smaller pN. Similar dependence was found for the networks with different mean connectivity p (see inset). Remarkably, the observed dependences could be well approximated numerically by the exponential dependence

$$\kappa_{cr} \propto (1 + pN)^L. \qquad (2)$$

As the second class, *asymmetric small-world networks* [15] were considered. To generate them, we first constructed a one-dimensional lattice of N elements, where each element had incoming connections from up to its kth neighbor (the degree was thus $2k$). Then, a randomly chosen link in the lattice was eliminated and a distant

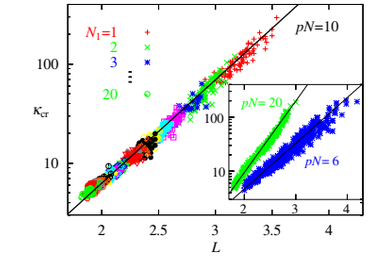

FIG. 2 (color online). Dependence of the entrainment threshold on the depth L for an ensemble of random networks with $N = 100$ and $p = 0.1$. In the inset, respective data for networks with $p = 0.06$ and 0.2 are plotted. Solid lines are the exponential functions $c_p(1 + pN)^L$ with appropriate fitting parameters c_p.

Main result

connection between two independently randomly chosen elements was introduced. This construction was repeated qN times, with the parameter q specifying the randomness of a network. After that, N_1 nodes of the network were randomly chosen and connected to one additional node representing the pacemaker. When q was small, the network was close to a lattice and, in this case, we have seen that stable wave solutions with different winding numbers were possible, depending on initial conditions (cf. [12,16]). To avoid this, we chose almost synchronized states as initial conditions. The entrainment thresholds for such small-world networks are displayed in Fig. 3 and again show a clear correlation between κ_{cr} and L. The dependence on the depth is approximately linear in lattices ($q = 0$), but it becomes strongly nonlinear even when small randomness is introduced. For $q = 0.1$, the dependence is already approximately exponential, though the dispersion of data is strong. As randomness q is increased, the dependence approaches that of the standard random networks with $pN = 2k$.

We have also investigated *asymmetric scale-free random networks* [17], *asymmetric regular random networks* (where every element has exactly the same number of either incoming or outgoing connections), and *symmetric standard random networks*. For all of them, approximately exponential dependences of the entrainment threshold on the network depth were observed in a large parameter region.

The exponential dependence (2) can be approximately derived for asymmetric random networks with large N and pN. In the large-size limit, random graphs have locally a treelike structure [14]. The global tree approximation has previously been used for determining statistical properties of random networks [17]. We apply here the same approximation and assume that the graph of forward connections extending from the pacemaker node represents a tree, so that any oscillator has only one incoming connection from the previous shell. Then the shell populations N_h are given by $N_h = N_1(pN)^{h-1}$ for $h = 2, \ldots, H$, where H is the total number of shells determined by $\sum_{h=1}^{H} N_h = N$. Because pN is large, we have $N_h \ll N_H \simeq N$ for $h < H$, and thus $L \simeq H$. Next, we estimate the numbers m_{hk} of incoming connections leading from all elements in the kth shell to an oscillator in the hth shell. By definition of hierarchical shells, $m_{hk} = 0$ if $k < h - 1$. In the tree approximation, $m_{hk} = 1$ for $k = h - 1$. Because most of the population is concentrated in the last shell, reverse connections from other shells can be neglected. On average, the number of reverse connections from the shell H to an oscillator in the shell h is $m_{hH} = pN_H$. Moreover, the relative statistical deviation from this average is of order $(pN)^{-1/2}$ and is thus negligible. Therefore, in this approximation, all oscillators inside a particular shell have effectively the same number of connections from other shells, and a state with phase synchronization inside each shell is possible. In this state, all oscillators inside a shell have the same phase, i.e., $\phi_i = \theta_h$ for all oscillators i in a shell h. Under entrainment, the phases of such a state can be found analytically as a solution of algebraic equations

$$-\frac{\kappa}{pN}\sum_{k=h-1}^{H} m_{hk}\sin(\theta_h - \theta_k) = 1 \quad \text{for} \quad h = 2, \ldots, n,$$

$$-\mu\sin(\theta_1 - \theta_0) - \frac{\kappa}{pN}\sum_{k=2}^{H} m_{1k}\sin(\theta_1 - \theta_k) = 1, \quad (3)$$

where $\theta_0 \equiv \phi_0$. For large pN, we can linearize $\sin(\theta_h - \theta_k)$ for $h, k \geq 2$ in the solution of Eqs. (3) [it can be shown that $\theta_2 - \theta_H$ is of order $O(1/pN)$]. Furthermore, using $N_H \simeq N \gg N_h$ for $h < H$ and $L \simeq H$, for $h \geq 2$ we obtain

$$\sin(\theta_{h-1} - \theta_h) = \frac{pN}{\kappa}(1 + pN)^{L-h}. \quad (4)$$

Eq. (4) determines the phases of oscillators in the considered synchronized state. Note that the explicit value of the phase θ_1 in this state is not needed below.

The entrainment breakdown can, in principle, occur through destabilization of the synchronized state. Though the analytical proof of its stability is not yet available, our numerical simulations show that the synchronous entrained state with $0 < \theta_{h-1} - \theta_h < \pi/2$ is always stable when it exists. Thus, the breakdown of entrainment in the considered system takes place in a saddle-node bifurcation, through the disappearance of solutions of Eqs. (3). This occurs when $|\sin(\theta_{h-1} - \theta_h)| = 1$ for certain h. For large enough μ, we always have $0 < \sin(\theta_0 - \theta_1) < 1$ (a sufficient condition is $\mu > 1 + \kappa$). Among the other terms, the term $\sin(\theta_1 - \theta_2)$ is always the largest one. Therefore, the solution disappears and breakdown occurs when $\sin(\theta_1 - \theta_2) = 1$. Substituting Eq. (4) into this equation and solving it with respect to κ, we finally derive the dependence (2). Thus, we see that the entrainment breakdown occurs through the loss of frequency locking between the first shell and the rest of the network. As seen in Fig. 2, the analytical dependence for the critical coupling strength, obtained using the tree approximation, agrees well with the numerical dependence, even for the networks which are not very large.

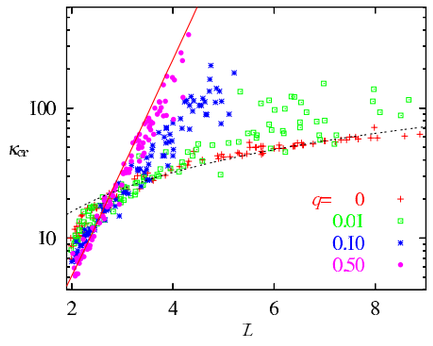

FIG. 3 (color online). Dependence of the entrainment threshold on the depth L for an ensemble of small-world networks with $N = 100$, $k = 3$, various N_1, $1 \leq N_1 \leq 20$, and different randomness q. The solid line is the same exponential function as that fitted to the data with $pN = 6(= 2k)$ in Fig. 2. The dotted line is linear fitting for the regular lattice ($q = 0$).

So far we have used the coupling strength which was rescaled as $\kappa \to \kappa/\Delta\omega$. Therefore, if the nonscaled coupling strength is fixed, Eq. (2) determines the maximum $\Delta\omega_c$ at which the entrainment is still possible, $\Delta\omega_c \propto \kappa(1 + pN)^{-L}$. The entrainment by a pacemaker can take place only if its frequency lies inside the interval $(\omega, \omega + \Delta\omega_c)$.

Thus, the entrainment window *decreases exponentially* with the depth of a network. This is the principal result of our study, which holds not only for standard random networks, where the above analytical estimate is available, but also for small-world graphs and other numerically investigated random topologies. In practice, it implies that only shallow random networks with small depths are susceptible to frequency entrainment.

Our results remain valid when, instead of a pacemaker, external periodic forcing acts on a subset of elements. We have checked that the reported strong dependence on the network depth remains valid for systems with larger network sizes, heterogeneity in frequencies of individual oscillators, and several other coupling functions. The study was performed for coupled phase oscillators which serve as an approximation for various real oscillator systems, including neural networks (see, e.g., [12,18,19]). Its conclusions should be applicable for a broad class of oscillator networks with random architectures.

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[1] A. N. Zaikin and A. M. Zhabotinsky, Nature (London) **225**, 535 (1970).
[2] A. T. Winfree, *The Geometry of Biological Time* (Springer, New York, 1980).
[3] K. J. Lee, E. C. Cox, and R. E. Goldstein, Phys. Rev. Lett. **76**, 1174 (1996).
[4] B. Blasius, A. Huppert, and L. Stone, Nature (London) **399**, 354 (1999).
[5] J. J. Tyson and P. C. Fife, J. Chem. Phys. **73**, 2224 (1980); M. Stich and A. S. Mikhailov, Z. Phys. Chem. (Frankfort am Main) **216**, 521 (2002).
[6] See, e.g., M. Stich, M. Ipsen, and A. S. Mikhailov, Phys. Rev. Lett. **86**, 4406 (2001); Physica (Amsterdam) **171D**, 19 (2002).
[7] R. Y. Moore, Ann. Rev. Med. **48**, 253 (1997).
[8] E. E. Abrahamson and R. Y. Moore, Brain Res. **916**, 172 (2001).
[9] S. Yamaguchi *et al.*, Science **302**, 1408 (2003).
[10] S. J. Kuhlman *et al.*, J. Neurosci. **23**, 1441 (2003).
[11] I. Z. Kiss, Y. M. Zhai, and J. L. Hudson, Science **296**, 1676 (2002).
[12] Y. Kuramoto, *Chemical Oscillations, Waves, and Turbulence* (Springer, New York, 1984).
[13] Note that the system (1) is invariant under transformation $\omega \to -\omega$, $\Delta\omega \to -\Delta\omega$, $\phi \to -\phi$, and therefore the same entrainment behavior takes place when $\Delta\omega < 0$.
[14] S. N. Dorogovtsev, J. F. F. Mendes, and A. N. Samukhin, Nucl. Phys. **B653**, 307 (2003); S. N. Dorogovtsev and J. F. F. Mendes, *Evolution of Networks: From Biological Nets to the Internet and WWW* (Oxford University Press, Oxford, 2003).
[15] D. J. Watts and S. H. Strogatz, Nature (London) **393**, 440 (1998).
[16] S. C. Manrubia, A. S. Mikhailov, and D. H. Zanette, *Emergence of Dynamical Order: Synchronization Phenomena in Complex Systems* (World Scientific, Singapore, 2004).
[17] M. E. J. Newman, S. H. Strogatz, and D. J. Watts, Phys. Rev. E **64**, 026118 (2001).
[18] Y. Kuramoto, Physica (Amsterdam) **50D**, 15 (1991).
[19] H. Kori and Y. Kuramoto, Phys. Rev. E **63**, 046214 (2001); H. Kori, Phys. Rev. E **68**, 021919 (2003).

Discussion

数値計算で得た結果の解析的な証明

参考文献

・「数理生理学」上：細胞生理学

J. Keener, J. Sneyd[著]　中垣俊之[監訳]

・高松敦子さん（早稲田大）の講義ノート

（WEBに公開されています）

お奨め本

・”Nonlinear Dynamics and Chaos”　S. Strogatz

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http://www.cf.ocha.ac.jp/acpro/kori/papers/suri_kagaku2011.pdf

郡宏、蔵本由紀：サイエンス社「数理科学」、2006年11月号
「連載：ネットワーク科学最前線」、第2回、「複雑ネットワークと非線形科学」

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郡宏：サイエンス社「数理科学」、2006年12月号
連載「ネットワーク科学最前線」、第3回、「振動子ネットワークの引き込みと体内時計」

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注意：変数の上に・がついていたら, それは時間微分.

例 $\dot{x} = \frac{dx}{dt}$, $\ddot{x} = \frac{d^2x}{dt^2}$