Universal Biology

Plan

March 6 Into+ alpha

Match 7   Methodology – examples of universal laws

March 8   Reproducing Cell, origin-of-life

March 9   Adaptation I

March 10 Wakamoto's pnline seminar (Adaptaion exp)   Adaptation II

March 13Evolution I

March 14 Evolution II   Pham's seminar

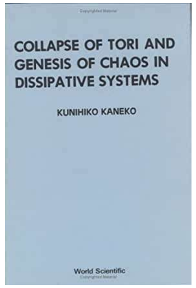
March 15 Development and Differentiation   Ritort's seminar

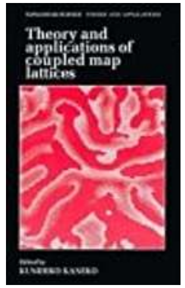
March 16 Furusawa's online seminar (evolution exp)   Memory

March 17 Exam

Brief Introduction of myself: Kuni Kaneko

Univ of Tokyo(Universal Biology Institute)
→ Niels Bohr Institute



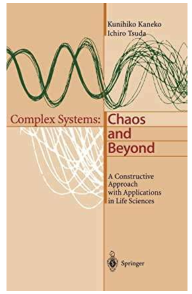


Research History:

Nonlinear Nonequilibrium (Stochastic Process)

→ Chaos

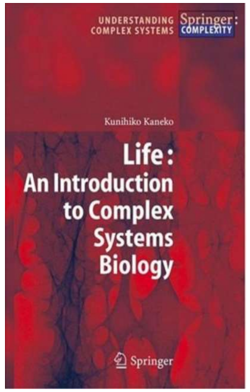
→Spatiotemporal Chaos (Coupled Map Lattice)

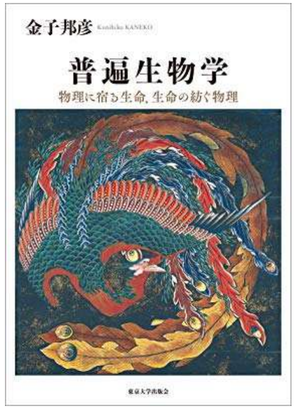


→Complex Systems; High-dimensional chaos (Globally Coupled Map)

→ Complex-systems Biology ;

Universal Biology

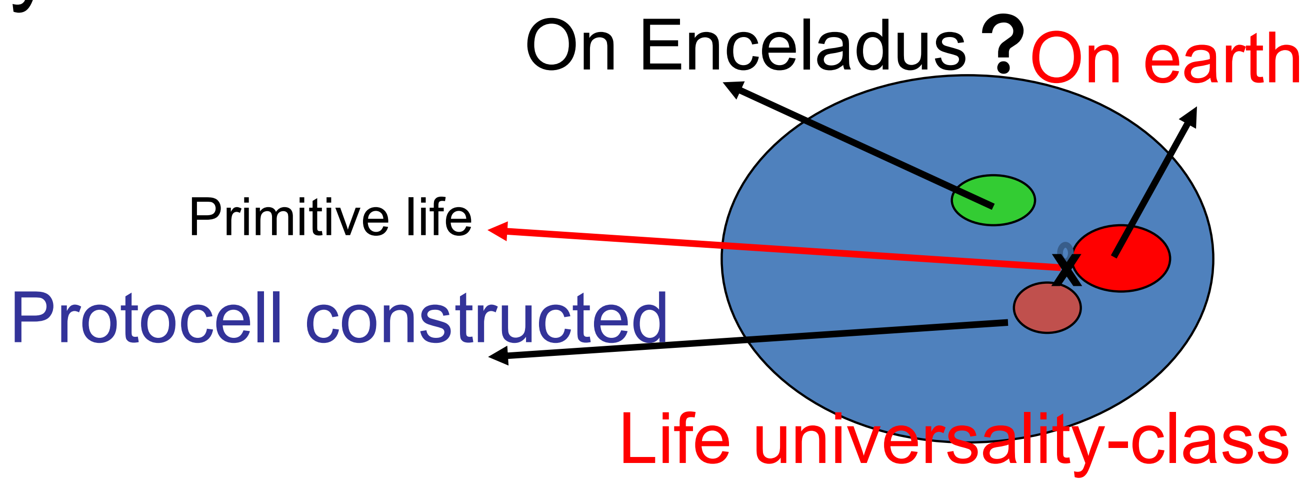




Universal　Biology

Life system as a universality class in nature
→
Phenomenological theory (a la thermodynamics)
→ general characteristics, universal laws

＊Biology not restricted to those that happen to be evolved on earth
(coined originally by SF writer
小松左京
(Komatsu Sakyo）
at 1968



Universal Biology – proposed? 1968 by Sakyo Komatsu (SF novelist)

- *Universal biology – science to explore universal patterns and possible variations of living organisms in this cosmos. It started to expand the end of last century (* i.e. 20c). Since then, characterization of life in terms of topological geometry (* dynamical systems?) has developed, and now, grand theory comparable to relativity is anticipated… ---*

Universal Biology Institute (in real world)
at Univ of Illinois and at Univ Tokyo

- Grand Challenge:

Cell --- very high-dimensional dynamical systems (~5000 proteins for bacteria etc.)

*(*why so diverse has to be addressed also)*

- Can we understand it?

Recall thermodynamics

(1) Restriction to equilibrium states (and transition between them)

(2) Microscopically; a huge number of molecules

(3) Macroscopically represented by few degrees of freedom – stability of eqb. system

- Thermodynamics was established before the existence of molecules was not established

0) Restrict to Equilibrium　States + Transition among them→　Description by few variables（Pressure,Temperature,)

1)Irreversibility → Odering→ Entropy S←→

2)Stability → Thermodynamic potential　F

3) Energy（consv）≠ Free Energy　F=E-TS

4) Equation of States

5) Le Chatelier principle（＜—stability, timescale)

6) Fluctuation-response　　　Einstein

7) Ideal Model (Carnot cycle, Ideal gas,,,)

- Universal Biology vs Thermodynamics (not theapplication of the latter)

0) Instead Restrict to steady-growth → each molecule replicated with the same rate

1) Robustness Waddignton's landscape

←Stability:Thermodynamic potential

0,1) Description by few degrees of freedom?

2) Irreversibility ：ES->Committed->..->Death

→ characterization to quantify ordering?

3) Activity instead of Free energy?

Growth: μ=Nutrient flow －loss

4) Equation of states?: transitions among exponential, stationary dormant phases

5) Le Chatelier's principle? (← consequence of stability, evoked (fast) change is compensated by (slower) response ←→ (adaption, evolution)

6) Fluctuation-Response relationship (plasticity (changeability) proportional to fluctuations)

7) Ideal Cell Model (a la Ideal gas)?

---- Difficulty / Difference Thd & UB----

- Many "kinds" instead of a large numbers?
- Micro-macro well separated? But consistency
- Inherently Dynamic? – oscillation,,,

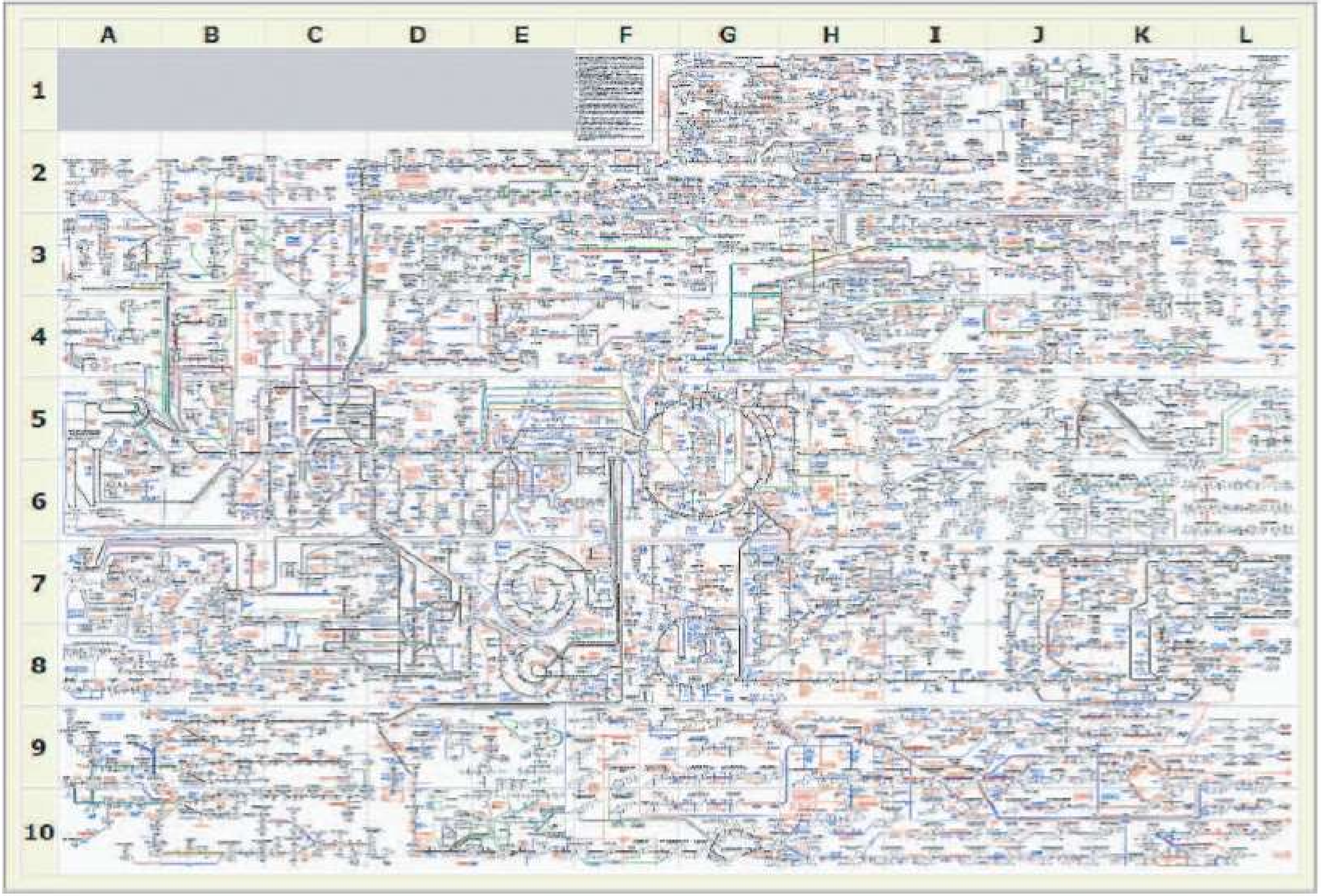
- Bio-universality
- Life ~ A system that consists of diverse components and that can continue to reproduce itself

- Diverse, but sustainable and reproducible

Not so easy

→Macroscopic robustness (homeostasis)

Complex Network + Fluctuation: how robust?

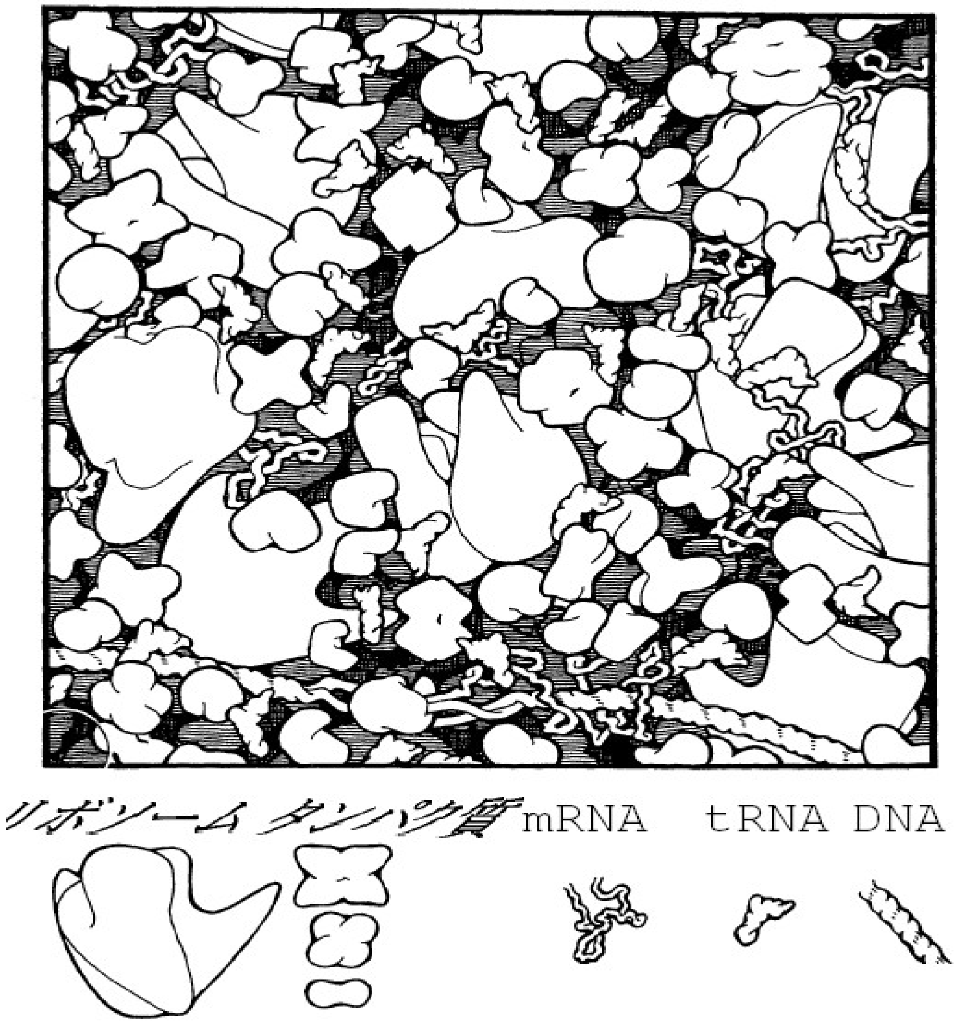


Metabolic Network of bacteria E coli (part)
Roche Tech page

Machine ———reduce interference among parts

Life(cell): Crowded, each part strongly interacts

cell→



Goodsell

Multicellular organism

Ecosystem

Society

(My) standpoint in Universal Biology

Life System consists of diverse components, maintains itself and can continue to produce itself

Guiding Principle-- Macro-Micro Consistency:

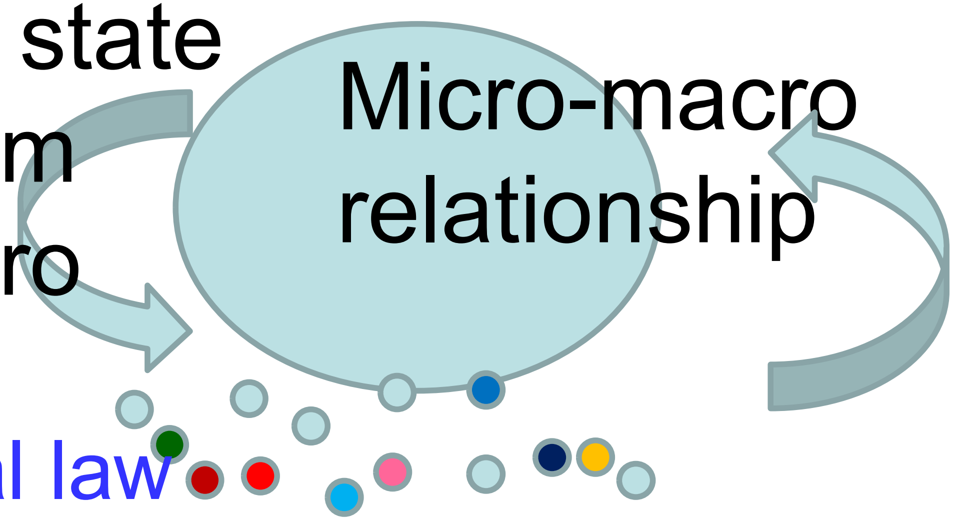
micro – diverse components (high-dimensional)
Thousands of chemical species

macro – unit to sustain/ reproduce as a whole (*low-dimensional description*?)

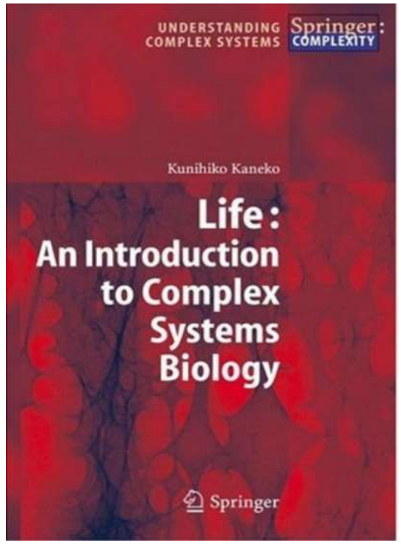
molecule – cell, cell-tissue etc.

Steady (growth) state

Constraint from macro to micro



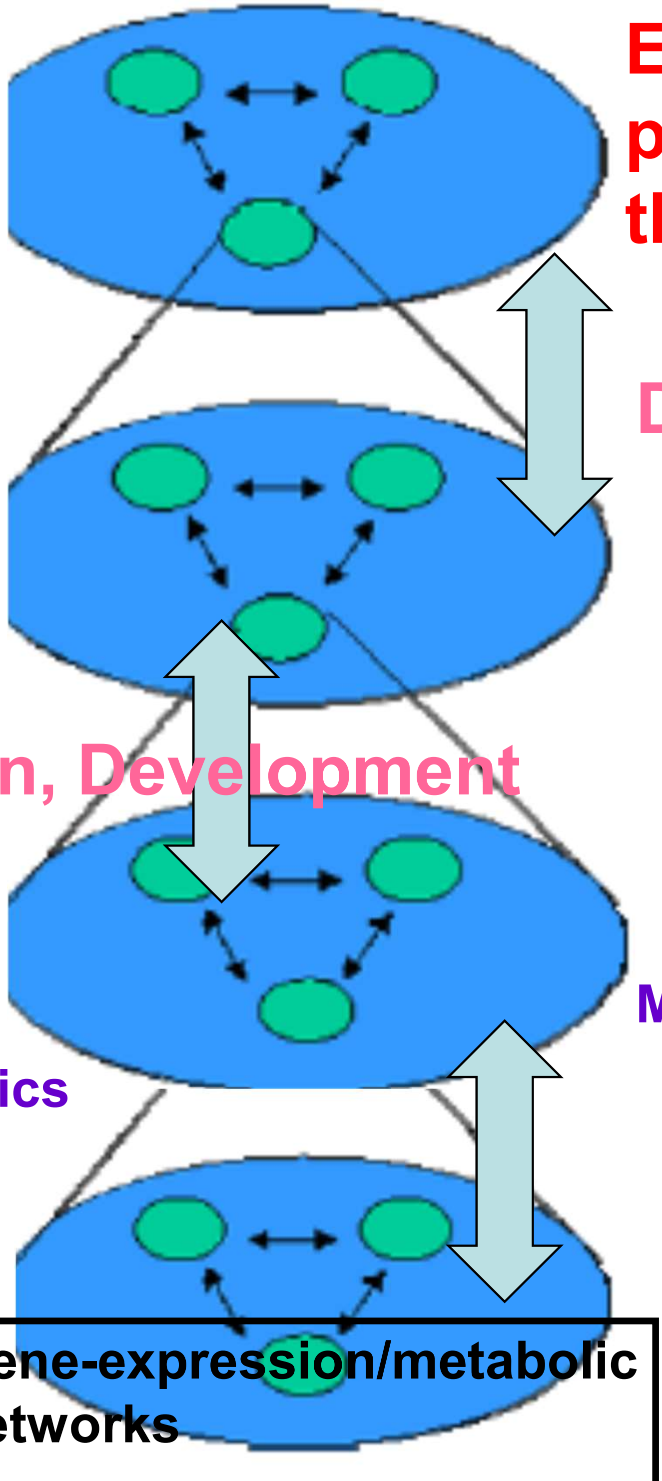
Universal statistical law



Complex-systems Biology

Consistency between hierarchical levels (+collapse)

Extract general basic properties of life, based on this consistency principle



Ecosystem

Diversity, Symbiosis

Multicellular organism

Cell-Tissue

Differentiation, Development

Evolution

Genotype ⟷ Phenotype

Cell

Cell-growth vs Intracellular dynamics

Molecule replication vs cell reproducti

Reproduction

Adaptation→

Molecule

Consistency with such distinct spatiotemporal scales?

- Consequence of a Reproducing System with diverse components

(1)Micro-macro Hierarchy:

micro – many components (high-dimensional)

macro – unit for reproduction as a whole (possibly described by few degrees of freedom)

(2) →Universal features?

reproduction, adaptation, diversification (differentiation), memory, evolution

→General law

(3)Macro-micro consistency--dynamic robustness

---Guiding principle

Consistency between dynamics of different levels

(1)Cell reproduction vs molecule replication →

universal statistical laws in gene expression

(Furusawa et al, PRL 2003,2012, Biophysics 2006,KK etal, PRX2015)

(2)Adaptation → universal adaptation laws (Kashiwagi et al Plos One2005; Furusawa, KK Phys RevE2018)

(3) Differentiation: **Cell vs multicellularity →**

Oscillatory dynamics => pluripotency + cell-cell interaction → differentiation, loss of pluripotency

(KK&Yomo 1997, Furusawa&KK,1998,Science 2012)

(4) Genetic vs phenotypic changes→

Isogneic Phenotypic Variance by noise ∝ variance by genetic change Vg ∝ Evolution Speed (plasticity)

Robustness to noise ~ to robustness to genetic change, (PNAS03,PLosOne07,Furusawa,KK,Interface2015,PRE 2018)

Consistency between different levels

(0) Different levels that mutually influence

(i)scale (time, space)

(ii)mechanism (physical, chemical,…)

(1)How are consistency formed (dynamics, evolution)

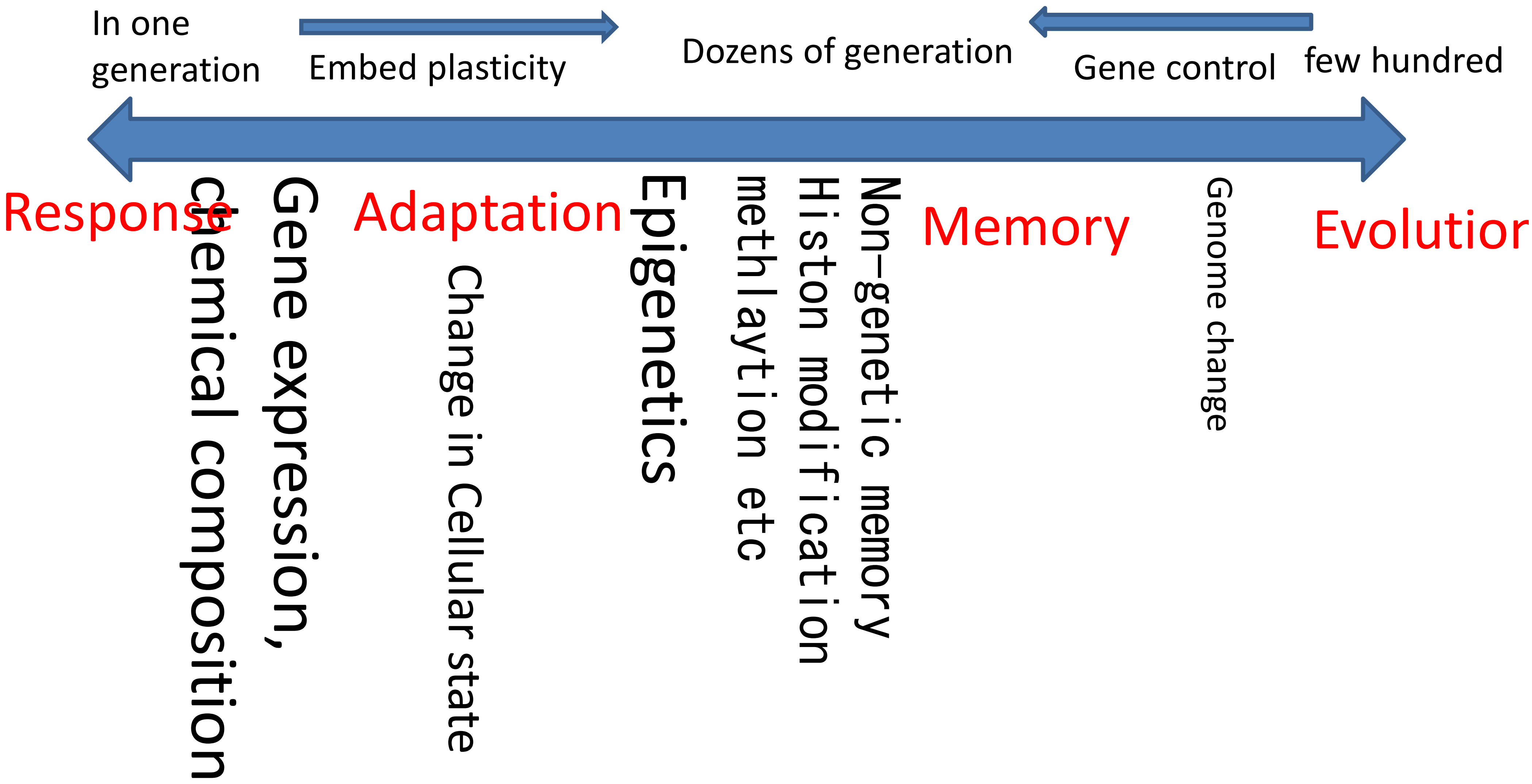
Consequence of Consistency Principle

* Separation of scales for robustness

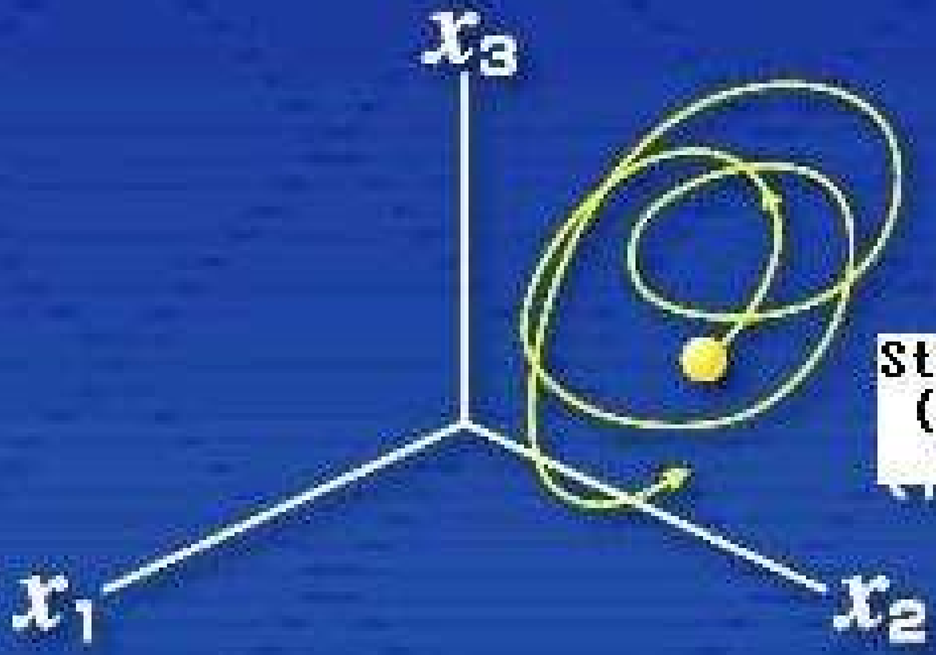
→Separation between control (slow) vs controlled (fast) : geno vs pheno (epigeno)

* Universal Statistical law for diverse microscopic elements (average, fluctuation) → law in reproduction, adaptation, evolution
* Discrete types for robust macroscopic states

Consistency among different Timescales



Dynamical Systems



State Space
(phase space)

State $\longrightarrow \{x_k(t)\}$

e.g., chemical concentration

dynamics $\longrightarrow$

$$\frac{dx_k}{dt} = f_k(\{x_j(t)\})$$

- Dynamical System

state – point in k-dimensional space

$x(1), x(2), \ldots, x(k)$ -- temporal change

Temporal evolution

determined by $\{x(1), x(2), \ldots, x(k)\}$

$dx(i)/dt = f_i(x_1, x_2, \ldots, x_k)$

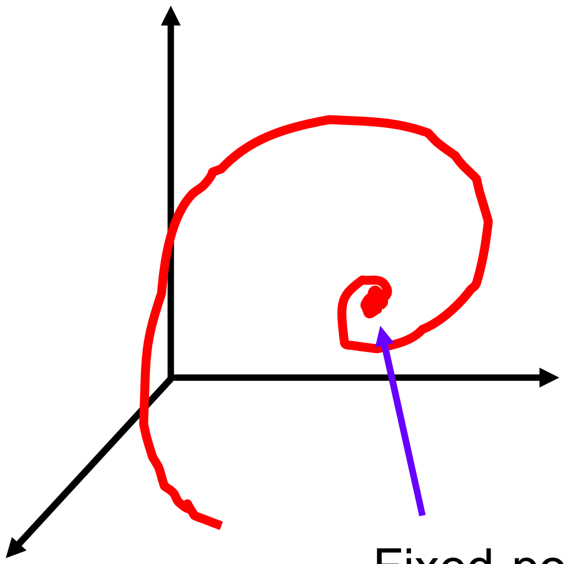
vector f_i on the state space determines the dynamics

With $t \to \infty$, $\{x_i\}$ reaches a certain region (nonwandering from it)

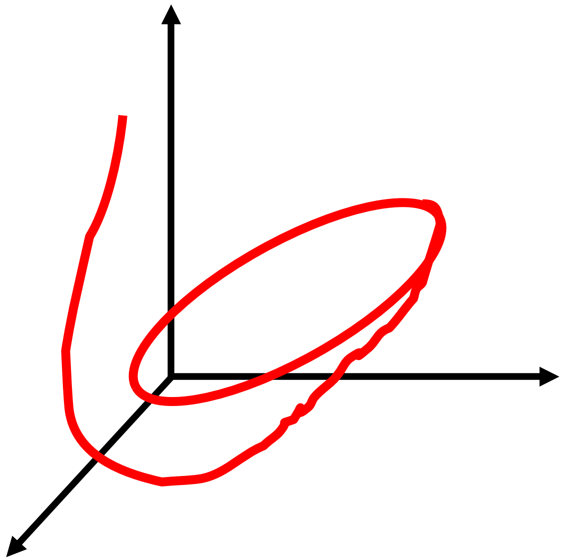
Attractor: The set of states that approach and stay for $t \to \infty$

attractor

After transients, the state reaches an attractor



Fixed-point attractor



Limit cycle attractor

(oscillating state)

Fixed Point Nullcline

dxi/dt=fi({xj})

dxi/dt=0

Nullcline, **set of points in which dx_i/dt=0 for given direction i**

fi({xj})=0

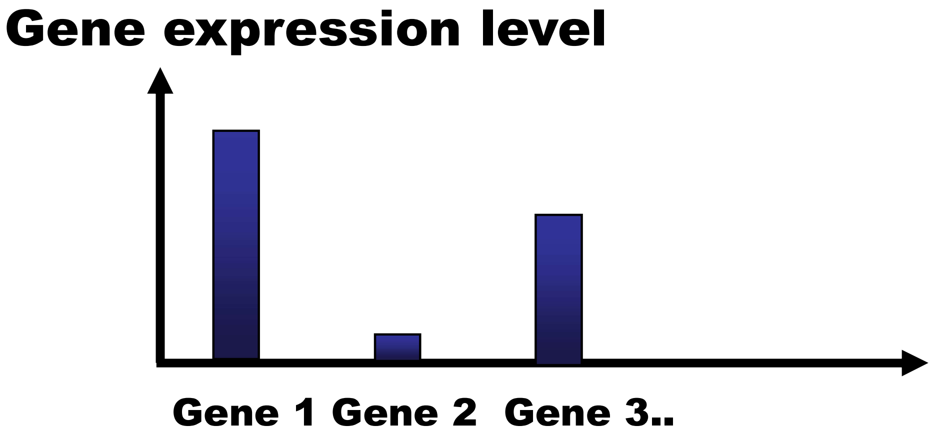
Fixed Point xi*=const. → dxi/dt=0

fi({xj*})=0

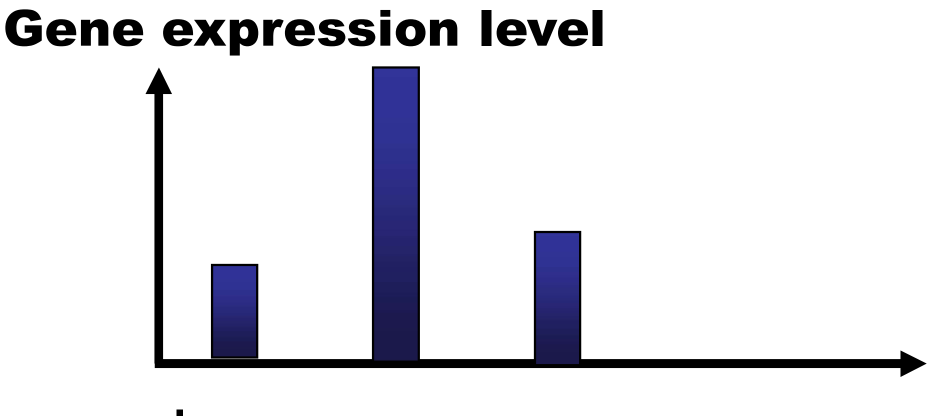
Intersection of nullclines

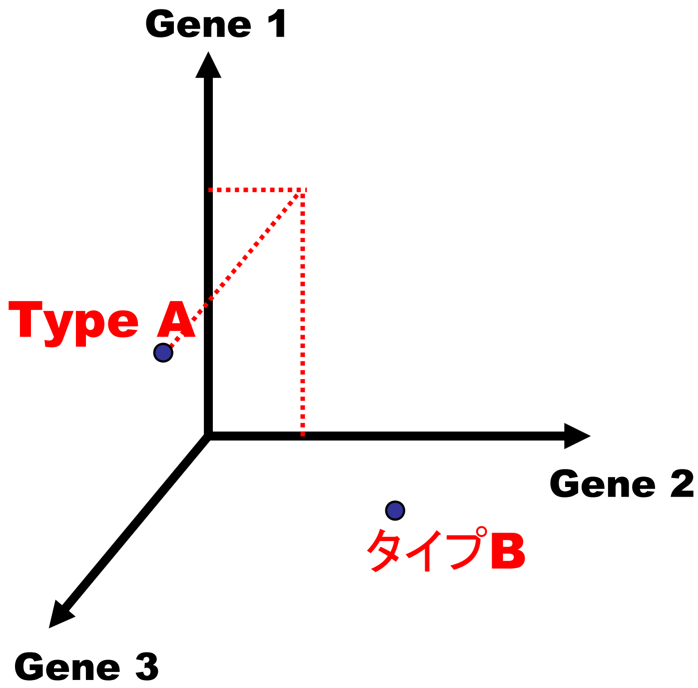
State representation of cells

Cell-type A



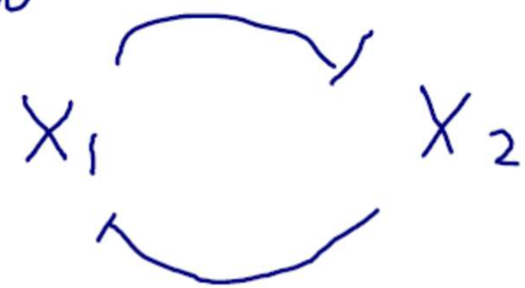
Cell-type B





Instead of mRNA, proteins, metabolites, ...

Toggle Switch



mutually suppress the expression

$$\frac{dm_1}{dt} = \gamma\left(\frac{\alpha}{1+p_2^2} - m_1\right), \quad \frac{dp_1}{dt} = m_1 - p_1$$

$$\frac{dm_2}{dt} = \gamma\left(\frac{\alpha}{1+p_1^2} - m_2\right), \quad \frac{dp_2}{dt} = m_2 - p_2$$

mRNA (m_i) ⋯ faster timescale $(\gamma \gg 1)$

adiabatic elimination $\longrightarrow \frac{dm_1}{dt} \approx 0, \ \frac{dm_2}{dt} \approx 0$

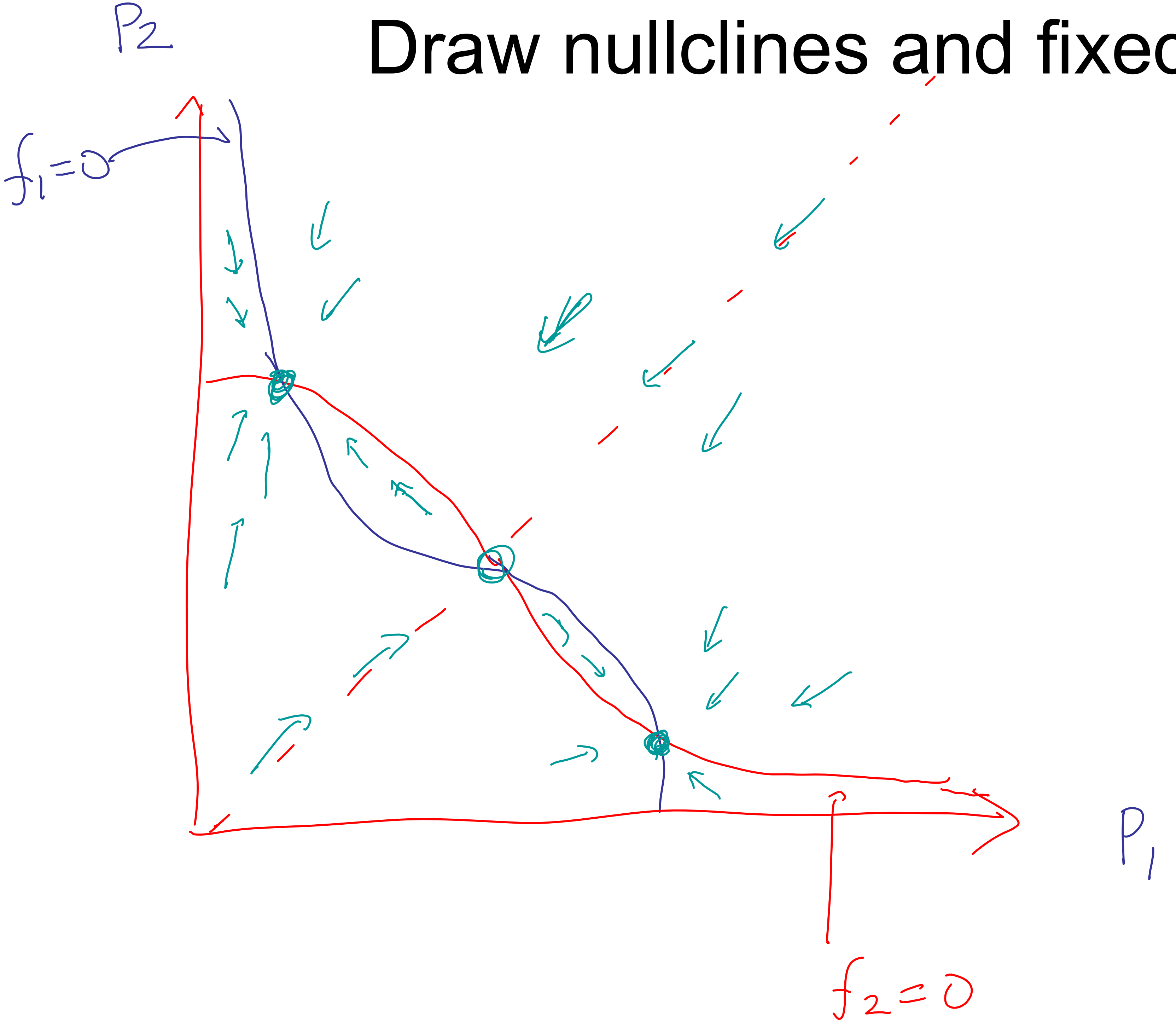
$$\frac{dP_1}{dt} = \frac{\alpha}{1+P_2^2} - P_1 \equiv f_1(P_1, P_2), \quad \frac{dP_2}{dt} = \frac{\alpha}{1+P_1^2} - P_2 \equiv f_2(P_1, P_2)$$

nullcline

$$f_1 = 0 \qquad P_1 = \frac{\alpha}{1+P_2^2}$$

$$f_2 = 0 \qquad P_2 = \frac{\alpha}{1+P_1^2}$$

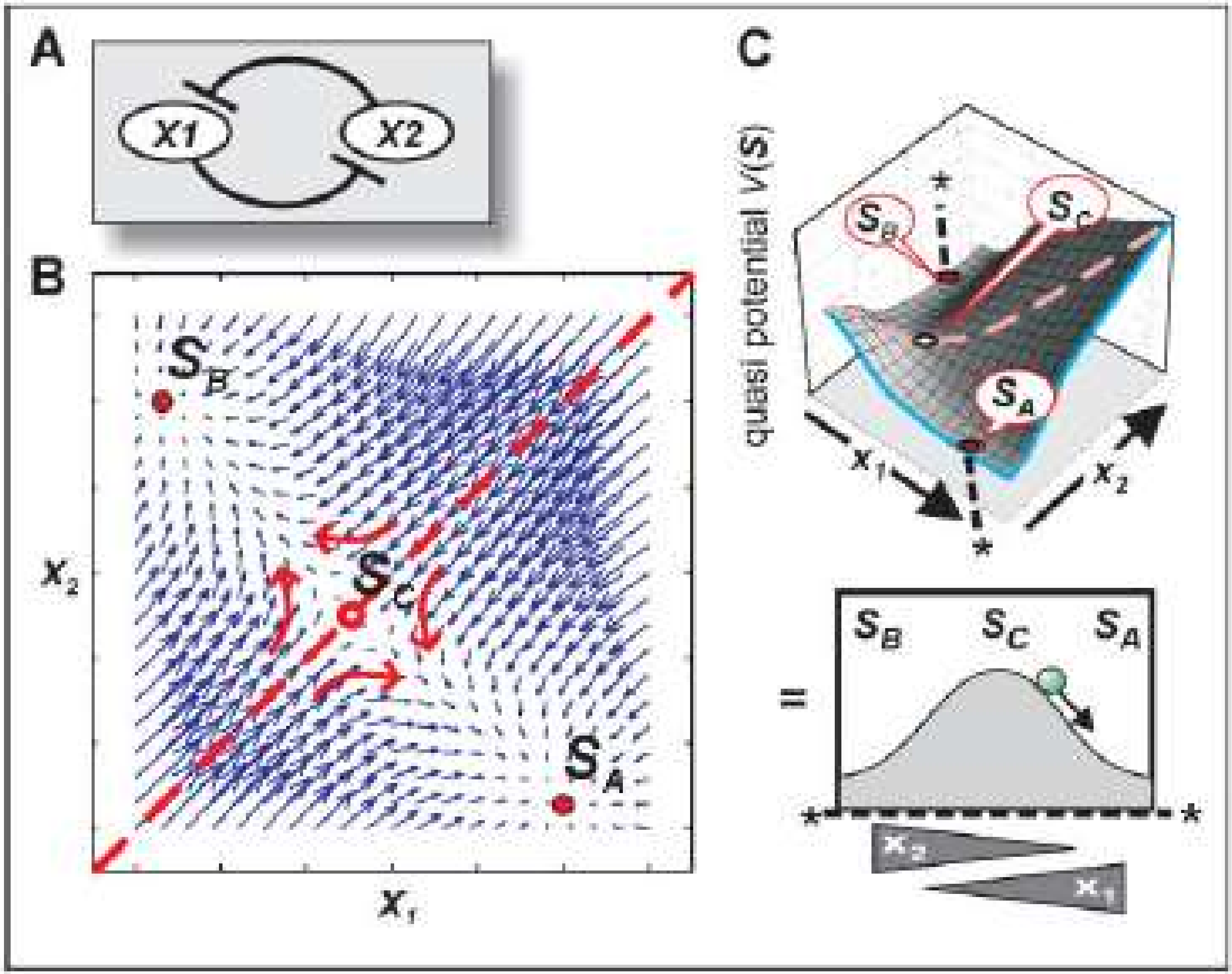
Draw nullclines and fixed points



固定点

Fixed point

Nullcline and fixed points



Sui Huang
Bioessay
2008

- Linear stability analysis

  dxi/dt=fi({xj}) $(i=1,2,\cdots k)$

  xi*=const. → dxi/dt=0

  fi({xj*})=0

  xi=xi*+δxi up to the order of δx

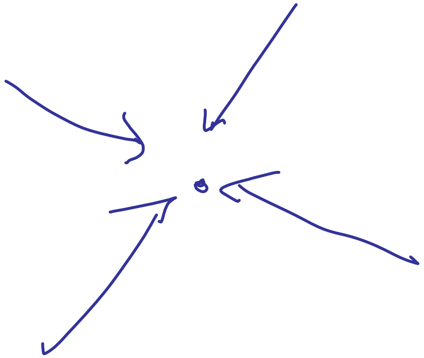
  Jacobi matrix $J = [J_{ij}]$

  $\delta \dot{x}_i = \sum_j J_{ij} \delta x_j$

J_{ij} の eigenvalues λ_i $i=1,\cdots,k$ $\rightarrow e^{\lambda_i t}$

$\mathrm{Re}\,\lambda_i < 0$ for $\forall i$ → stable

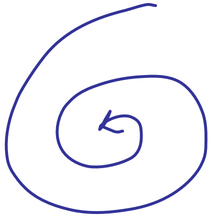
$\mathrm{Im}\,\lambda_i = 0$



sink

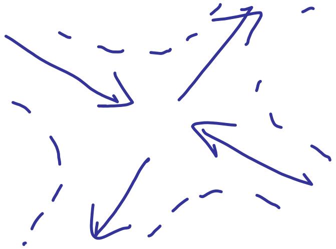
$\mathrm{Im}\,\lambda_i \neq 0$ $\lambda_i = \alpha \pm i\omega$, $\alpha < 0$

$e^{\alpha t}\, e^{\pm i\omega t}$



焦点 focus

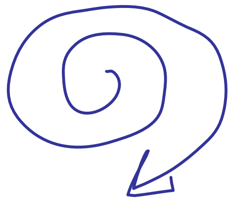
$\mathrm{Re}\,\lambda_i > 0$, $\mathrm{Im}\,\lambda_i = 0$



saddle 鞍点

$\mathrm{Im}\,\lambda_i \neq 0$

$\mathrm{Re}\,\lambda_i > 0$



method

1 Macro phenomenology: representation by few degrees

2 Micro high-dimensional : statistics

3 Macro-micor-cosnsitency

(cf fluctuation-response, ala Einstein, Kubo,..)

4 Time-scale consistency

(eg., enzyme abundances regulate timescale)

(homeostasis,memory)

5 breakdown of consistency?

Constructive (vs synthetic) biology

→ face with hierarchy, many degrees of freedom

learn from deviation from designed behavior