Universal Biology Project

Overview

Universal biology is an interdisciplinary approach to biology in the spirit of physics.

Life systems, in general, consist of diverse components and maintain themselves and can reproduce themselves. It is hierarchical in nature, as molecule, cell, organism, and ecosystem。 It is marvelous that the system with such diverse components (e.g., molecule species, cell types, species) achieves robustness to perturbations, sustaining itself and reproducing itself.

Guiding principle here is **consistency between different levels** – e.g., a cell reproduces itself whereas molecules, every component within also has to be replicated in correct proportions, to keep the composition of each. In spite of huge differences in scales (say molecule vs cell, cell vs individual), the changes in each scale must keep strong correlation. Following this **macro-micro consistency principle**, we uncover *evolutionary dimension reduction*; even though components in a biological system are huge (*high-dimensional*), their adaptive changes are strongly constrained (into a low-dimensional space). By recalling that such reduction with the micro-macro consistency is also the basis on the statistical physics and thermodynamics, we aim to formulate general laws and uncover universal properties in adaptation in cellular systems, development with differentiation, resilient ecosystems and evolution.

Conceptual Questions to be addressed

(1) How are biological **robustness** (unchangeability) and **plasticity** (changeability) compatible?

(2) Does the constraint of consistency between different scales lead to universal characteristics or general laws in cellular and developmental processes, evolution, and ecosystems?

(3) Is there a biological consequence of breakdown of consistency between micro and macro scales, which, for example account for cancer states, novelty evolution, or collapse of ecosystems?

This interdisciplinary project is in tight collaboration with **Biocomplexity group (Center for Models of Life) at Niels Bohr Institute**, and UCPH. Internationally, we establish tight collaboration with **Universal Biology Institute at University of Tokyo**, Japan.

State of the art

While molecular biology has shed light on the details of each element in life, how a robust and plastic life system can be formed from a complex dynamic network with a huge variety of elements remains unanswered. Now, it has become possible to measure the concentration of a huge variety of components by transcriptome and proteome analysis. How to characterize the living state from this enormous data remains to be a big issue, which requires novel frameworks based on statistical physics and dynamical systems.

Biosystems consist of hierarchical levels, molecules, cells, individuals, ecosystem. Here, an important point is consistency between different levels – for example, a cell reproduces itself whereas molecules, every component within also has to be roughly doubled, to maintain the composition of each.

In Universal Biology, based on such consistency between micro- and macroscopic levels (say molecule, cell, organism,), we have derived general laws in adaptation in cellular systems. They include power-law statistics in chemical abundances in cells, log-normal distribution of protein concentrations on cell-cell variation, correlated changes across thousands of gene expressions, linear relationship between phenotypic fluctuations and evolution speed of phenotypes, as confirmed experimentally.

Following these studies on consistency across scales, the *evolutionary dimension reduction* hypothesis is proposed: Even though the number of components in a cell is huge (*high-dimensional*), their possible changes by adaptation and evolution are restricted within a low-dimensional space. The fitted robust cellular states can move only within the low-dimensional space. Several simulations and some experimental data support the hypothesis.

If the dimension reduction is valid, it will enable to express adaptive, developmental, and evolutionary changes of biological states (say cellular states given by a huge set of chemical concentrations) by few variables. One can understand robustness-plasticity relation: the system returns to the original state quickly for most perturbations out of the low-dimensional space, implying the robustness, whereas the dynamics along this low-dimensional space is much slower and provide the plasticity.

Research Objectives

Four basic conceptual issues to be addressed:

(A)**Diversity and Multilevel Consistency:** How is such huge diversity in elements (molecules, cells, species) sustained under external perturbations? Are basic characteristics of cells (compartmentalization, separation between function and heredity) a necessity of reproducing systems? How is consistency across different scales with diverse components achieved? Does the constraint of consistency lead to universal characteristics or general laws in developmental processes, evolution, and ecosystems?

(B)**Robustness-Plasticity**: Biological systems are robust to noise and changes in external environment, while they are plastic to adapt to such changes. How are robustness (unchangeability) and plasticity (changeability) compatible? How are the plasticity (and evolvability) and robustness represented in terms of dynamical systems and statistical physics?

(C)**Theory of Multi-level Consistency and Dimension Reduction**: Can we generally formulate it, beyond specific models or experiments, to support universality in all biological systems?

(D) **Consequence of Breakdown of Consistency**: What is the consequence of the breakdown of consistency, say novelty evolution, aberrant states like cancer, collapse of ecosystems?

Four research topics:

I) Universal Characteristics in Cells and Theoretical Foundation of Universal Biology:

Questions: How is robust reproduction of cells achieved and sustained from just an ensemble of diverse chemical reactions? How is the transition from growing to non-growing states achieved? How can cells adapt to a huge variety of environmental conditions (including unforeseen changes)? How can cells memorize the previously experienced conditions?

i)Characterization of Transition from Exponential Growth Phase to Stationary (Non-growing) Phase
ii)How is dimensional reduction from high-dimensional states to low-dimensional phenotypes achieved through adaptation?
iii)How consistency with processes between macro/micro (slow/fast) scales achieved?
iv)Generation of memory as embedding of fast changes to slower changes (e.g. gene-expression to epigenetic modifications)
v)Statistical-Physics Theory for Dimensional Reduction

II) General Constraint and Universal Characteristics in Evolution:

Questions: Is there a direction and constraint in phenotypic evolution? Is there some correlation between short-term adaptation and long-term evolution, as recent studies suggested? If so, how is it possible? Can we control the evolution in a laboratory? How does the diversification of phenotypes progress? How is evolution of novelty and speciation achieved?

i)*Direction and Constraint in Phenotypic Evolution:*
ii)*Macroscopic Potential to Predict Phenotypic Evolution*:
iii) Establishment of evolutionary fluctuation-response theory

III) **Universal Characteristics in Development**:

Questions: *How is diversification of cell types coordinated, and how is robust development achieved within the huge diversity of molecules and cells? How is irreversible differentiation characterized? How is cellular-tissue consistency achieved? What happens if this consistency is broken? How can we control the developmental process, is there limit to reprogramming to gain the multipotency?*

i)Dynamical-systems representation of *irreversible differentiation from stem cells, together with epigenetic changes*: ro**bustness in developmental processes;** *Explicit construction of epigenetic landscape with homeorhesis; Theory for reporgramming:*
ii)Theory for Cancer state as breakdown of the multicellular consistency:
iii) *Evolution-development Congruence:*

IV) **Dynamics, sustainability, and evolution of ecosystems**:

Questions to be addressed: *how does diversification progress? How is resilience of ecosystem achieved? What perturbation will destroy the ecosystem to lose the diversity, and how can one control the ecosystem to regain diversity?*

(i): *Dynamics of interacting heterogeneous cells allowing for coexistence of diverse cells with distinct genotypes:*
(ii) *Evolution of an ecosystem to keep diversity*: consistency between macroscopic (ecosystem) and microscopic levels (organisms), Eco-Devo relationship [7].

Methods

- Dynamical Systems Model with Catalytic Reaction Networks/Gene Regulation Networks
- Evolution Simulations
- High-dimensional Dynamical Systems
- Dynamical Systems with Plastic/Diverse Time Scales
- Stochastic Processes
- Multilevel-Dynamics and Multi-level evolution (Molecule-Cell-Organism-Ecosystem
- Statistical Physics Theory for Dimensional reduction

Selected References

See also

http://chaos.c.u-tokyo.ac.jp/study/study-list.html
https://scholar.google.co.jp/citations?hl=ja&user=X9ffPWMAAAAJ&view_op=list_works&sortby=pubdate

K.Kaneko "Life: An Introduction to Complex Systems Biology", Springer 2006)； "Universal Biology" (U Tokyo press, 2019, 322pages, so far in Japanese)

Dimensional Reduction

K.Kaneko, C.Furusawa, (2018) Annual Rev. Biophys. 47, 273-290
C.Furusawa, K.Kaneko (2018)"Formation of Dominant Mode by Evolution in Biological Systems" Phys. Rev. E 97; 042410
K.Kaneko, et al., (2015) "Macroscopic phenomenology for cells.. ", Phys.Rev.X 5;011014
A. Sakata, K. Kaneko, (2020) "Dimensional reduction…"Phys. Rev. Lett.　124, 218101

Universal Characteristics of Cells

C. Furusawa, K.Kaneko,(2003)"Zipf's law in gene expression"Phys.Rev.Lett. 90, 088102
C. Furusawa, .., K.Kaneko,(2005)".. log-normal distribution in intra-cell..", Biophysics, 1, 25
C.Furusawa, K.Kaneko (2012)"Adaptation to optimal cell growth.."Phys. Rev. Lett., 108, 208103;(2008)"..Adaptive growth.." PLoS Computational Biology, 4, e3
M.Hashimoto,, K.Kaneko,.Y. Wakamoto (2016)"Noise-driven growth rate gain in clonal cellular populations"PNAS 113, 3251-3256
Y. Himeoka, K. Kaneko (2017) "Theory for transitions between exponential and stationary phases: universal laws for lag time"　Physical Review X,(2017) 7, 021049
N. Takeuchi & K. Kaneko (2019) " The origin of the central dogma through conflicting multilevel selection"　Proceedings of the Royal Society B, 286(1912), 20191359.

Evolution

K.Sato,,, K.Kaneko (2003)".. Relation between Fluctuation and Response in Biological Systems", PNAS 100;14086-14090
C.Furusawa, K.Kaneko (2015) ".. Fluctuation and Response in Adaptive Evolution", J of Roy.

Soc. Interface 12, 20150482
K.Kaneko,(2007) "Evolution of Robustness to Noise and Mutation..”PLoS One,2 e434

Cell differentiation and Development

C.Furusawa, K.Kaneko (2012)“A Dynamical-Systems View of Stem Cell Biology”, Science 338;215-217
C.Furusawa, K. Kaneko(2001)“Theory of robustness of irreversible differentiation in a stem cell system..”, J. Theor. Biol. 209, 395-416; (2011) N. Suzuki,,, K.Kaneko,”Oscillatory..” PLoS One, 6, e27232
Y. Matsushita, K. Kaneko (2020)”Homeorhesis in Waddington's landscape..”. Phys.Rev.Res. 2, 023083
K. Kaneko (2011).”Characterization of stem cells and cancer cells..” Bioessays, 33, 403-413
T.Kohsokabe, K.Kaneko (2016)“Evolution-Development Congruence..” J. Exp Zoology B 326; 61-84

Ecosystem

J.F. Yamagishi, N.Saito, K. Kaneko (2020) Phys. Rev. Lett. 124; 048101; PLoSCB 2021