Bioinformatics

Mathematical biology

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http://www.bioplexity.org/lectures/

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Mathematical descriptions in biology

Mathematical modelling and simulation ways in biology.

- qualitative and stochastic descriptions.
- structures, dynamics, stability, changes.

Main topics

- mathematical dynamics
  - qualitative differential equations
  - stability, stochastic systems
- populations and organisms
  - cells, tissues, tumors, evolution
  - neuronal systems, cognition
- molecular systems
  - structures and networks
  - chromatin, enzymatic pathways

Mathematical description

- biology in silico
  - mathematical biology
  - computational biology
  - theoretical biology
- approaches
  - stochastic vs. deterministic
  - symbolic vs. numerical
  - qualitative vs. quantitative
- objects
  - systems: abstract vs. concrete
  - structures: static vs. dynamical
  - time: discrete vs. continuous

Biological abstraction

biologists point of view

- description levels
  - supracellular description
  - subcellular description
- concreteness
  - specific individuum
  - multi-unite system
- questions for
  - structural localization
  - time development

Development rules

biological non-linearity grounds

- codes
  - strings: replication, translation
  - rules fixed in evolution
    - genetic code, histone and suger hypotheses
- attractors
  - non-linear dynamics
  - 'rivers with their basins'
    - codes for attractor development
- states
  - machine abstraction
  - development stages
    - states based regulation modes

Attractor terrain

attractor basin

attractor mutations

Dynamical systems

- study
  - experiments
    - bioinformatics explorations
  - computations
    - molecular modeling
  - theory
    - model development and characterization

- phase flows: $\vec{q}'(t) = \vec{N}(\vec{q}(t), t)$
  - continuous time
  - differential equations
  - (non)integrable systems
- phase maps: $\vec{q}_{n+1} = \vec{f}(\vec{q}_n, t_n)$
  - discrete time
  - difference equations
  - recurrence relations

Dynamics properties

- linearity
  - linear systems
    - total system as a fixed sum of its subsytems
    - superposition: el.-mag., quantum systems
  - non-linear systems
    - without overall description on independent parts
    - open systems, approximated descriptions
- integrability
  - integrable systems: with solvable phase flow equations
    - regular systems
    - in Hamiltonian physics - with constants of motion
      $\longrightarrow$ simple dynamics
  - non-integrable systems
    - usually chaotic systems

Phase volume

phase spaces - state spaces, variables as dimensions

- Hamiltonian systems
  - having a function $H = H(q_1, ..., q_k, q_{k+1}, ..., q_{2k})$
    where for $i \in 1, ..., k$: $N_i = \partial H / \partial q_{k+i}$, $N_{k+i} = -\partial H / \partial q_i$
  - then $\nabla \vec{N} = 0$, i.e. zero divergence of $\vec{N}$
    in return we have constant phase volume

- Ergodic systems
  - dynamical systems with constant phase volumes
  - having the phase space of finite phase (Liouville) volume,
    'every' point of a subset returns back (inifinitely many times)
  - however the return time grows fast for the particle count

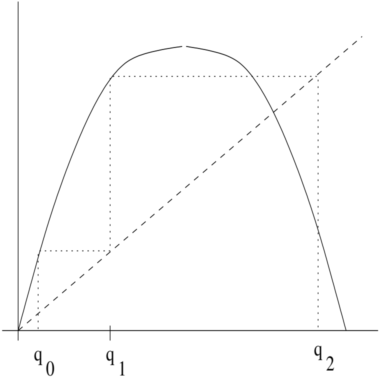
Orbits - trajectories

autonomous dynamical systems

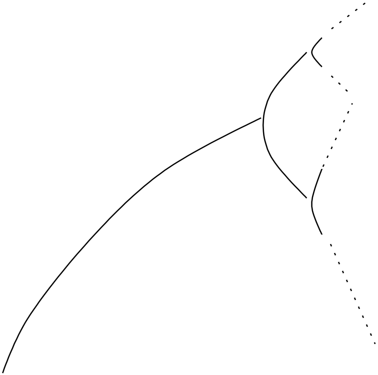
- fixed points
  - discrete systems: $\vec{q} = \vec{f}(\vec{q})$
  - continuous systems: $\vec{N}(\vec{q}) = 0$
- periodic orbits
  - discrete systems: $\vec{q} = \vec{f^k}(\vec{q})$
  - continuous systems: $\vec{q}(t + T) = \vec{q}(t)$
- stability
  - ds: $|f_i'(\vec{q})| < 1$, $\prod_{j=0}^{k-1} |f_i'(\vec{q}(j))| < 1$
  - cs: real parts of roots of $|L_{ij}(\vec{q}) - \lambda I| = 0$ are lesser than 0, where $L_{ij} = \partial N_i(\vec{q})/\partial q_j$

Logistic map

- definition: $q_{n+1} = f_a(q_n) = a \cdot q_n(1 - q_n)$
- fixed points
  - solution: $p_0 = 0$, $p_1 = 1 - 1/a$
  - p_1 stability: for $a \in (1, 3)$
    - $f_a'(q) = [a \cdot q(1 - q)]' = a[(1 - q) - q] = a(1 - 2q)$
    - $f_a'(p_1) = 2 - a$
- periodic (two steps) points
  - solution: $p_{3,4} = 1/2 \cdot (1 + 1/a \pm 1/a \cdot (a^2 - 2a - 3)^{0.5})$
  - stability: $a \in (3, 1 + \sqrt{6})$
- bifurcation
  - periodicity of stable periodic point going to ∞ with $a \rightarrow 4$
  - chaos for $a = 4$, with $q_n = \sin^2(2^n \arcsin(\sqrt{q_0}))$



web diagram



bifurcations

Chaos introduction

systems with 'butterfly effects' alleged

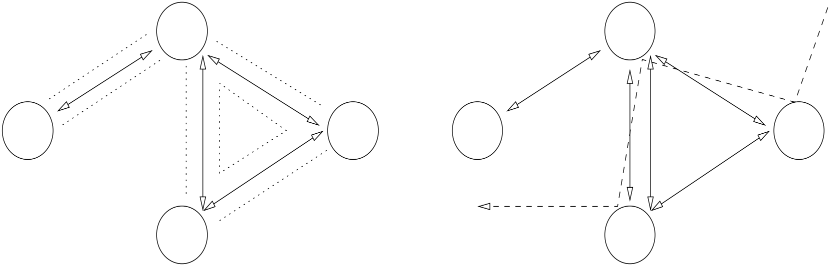
any viewable butterfly effect would be 'privileged'

- chaos properties
  - sensitive to initial conditions
  - with topological mixing
  - with dense periodic orbits
- chaos onset
  - common case: subsequent bifurcations
  - Feigenbaum constant $\delta = 4.669201609...$
    - limit of ratios of bifurcation $n - th/(n+1) - th$ intervals
- attractors
  - fractal dimansionality $dim =$
    - log(number of self-similar pieces) / log (magnification factor)

issues in chaos and dynamics

- classical chaos
  - summations on periodic orbits
    - trajectories in neighborhoods of the (dense) periodic orbits
    - an analogy to the most probable states of statistical physics
- dynamics classes
  - KAM theorem
    - invariant tori that 'survive' weak non-linear perturbations are those with irrational / non-resonance frequencies
  - FPU systems
    - computations on coupled oscillators
    - excitations on single ones, occasional jumps
  - famous systems
    - Brownian dynamics: path of dimension 2 (for R^n, $n > 1$)
    - patterns of reaction-diffusion systems

deterministic chaos explorations

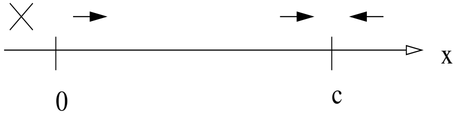


- system characterization by periodic orbits
  - periodic orbits are dense for chaotic systems

Logistic curve

simple population growth

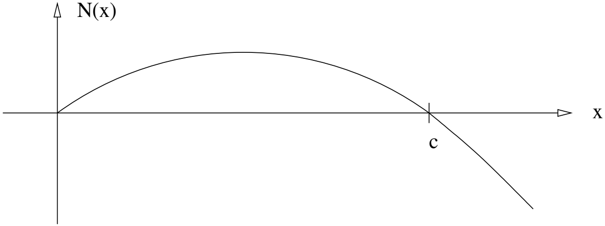
- $dx/dt = r \cdot x \cdot (1 - x/c)$, with $r, c > 0$
  - one-dimensional continuous dynamics
  - fixed points are 0 (extinction) and c (stable)
  - more simple dynamics than for the discrete case
    - general fact: difference equations harder to solve than differential ones
  - solution $c \cdot e^{rt}/(e^{rt} + s)$
    where $s = 1 - c/x_0$ for $x_0 = x(t = 0)$



Graphical description

how to analyze fixed point stability

- logistic growth
  - $L_{11}(x = c) = \partial[r \cdot x \cdot (1 - x/c)]/\partial x|_{x=c}$
    $L_{11}(x = c) = r \cdot (1 - 2x/c)|_{x=c} = -r < 0$
  - i.e. it is a stable fixed point
  - it is mouch easier to see it from the fact that $\dot{x} > 0$ for $x < c$ and $\dot{x} < 0$ for $x > c$



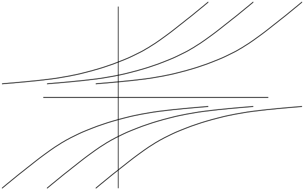
Differential equations

general properties

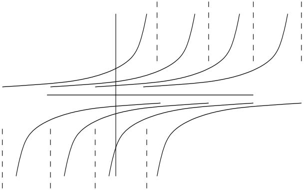
- situations
  - one x or two x, y variables depending on themselves
  - development in time: dx/dt, or dx/dt, dy/dt
- $dx/dt = f(x, t)$, with $x(t_0) = y_0$
  - solution existence
    - $f(x, t)$ is continuous
  - solution uniqueness
    - both $f(x, t)$ and $\partial f/\partial x$ are continuous
- autonomous systems for x and y
  - $dx/dt = f(x, y)$
  - $dy/dt = g(x, y)$
  - frequently the case for biological systems

1-dimensional problems

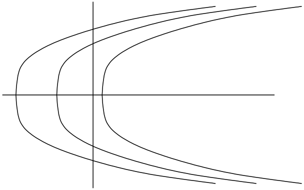
simple autonomous systems $dx/dt = f(x)$



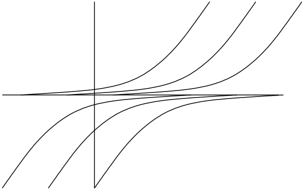
$f(x) = x$ ... $x \sim e^t$



$f(x) = x^2$ ... $x \sim 1/|t|$



$f(x) = 1/x$ ... $x \sim \sqrt{|t|}$



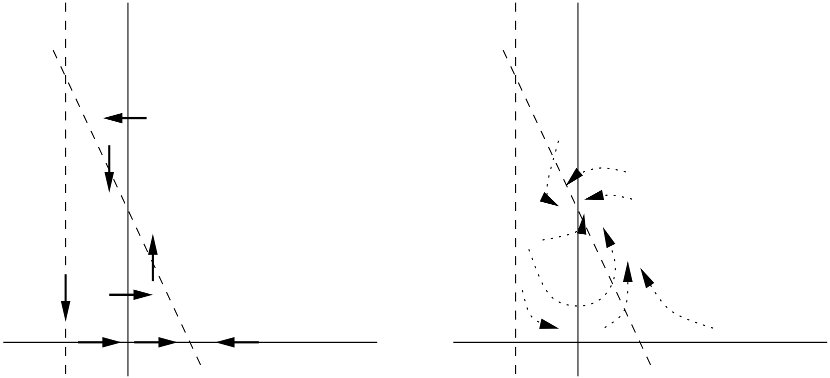
$f(x) = \sqrt{|x|}$ ... $x \sim t^2$

Qualitative description

qualitative differential equations

- 2-dimensional autonomous systems
  - $dx/dt = f(x, y, t) = f(x, y)$
  - $dy/dt = g(x, y, t) = g(x, y)$
  - to plot phase portraits of the systems and to predict their dynamics
- solution methods
  - 1) null-cline analysis
    - where $f(x, y)$, $g(x, y)$ are zero valued
  - 2) Jacobian analysis
    - types (stability) of fixed points
    - a) determinant-trace method
    - b) graphical Jacobian

- phase portraits
  - $dx/dt = 3x(1-x) - 1.5xy$ ... zero - dashed lines
  - $dy/dt = 0.5xy - 0.25y$ ... zero - solid lines



Jacobian method

stability of fixed points

- computations for a fixed point $\bar{x}, \bar{y}$
  - $detJ = (\partial f/\partial x \cdot \partial g/\partial y - \partial f/\partial y \cdot \partial g/\partial x)|_{\bar{x},\bar{y}}$
  - $trJ = (\partial f/\partial x + \partial g/\partial y)|_{\bar{x},\bar{y}}$
  - $D = (trJ)^2 - 4(detJ)$
- particular cases
  - $detJ < 0$ saddle point [the $\{0, 0\}$ and $\{1, 0\}$ cases]
  - $detJ > 0$, $trJ > 0$, $D \geq 0$ non-stable node
  - $detJ > 0$, $trJ < 0$, $D \geq 0$ stable node [the $\{0.5, 1\}$ case]
  - $detJ > 0$, $trJ > 0$, $D < 0$ non-stable spiral
  - $detJ > 0$, $trJ < 0$, $D < 0$ stable spiral
  - $detJ > 0$, $trJ = 0$, center point

Symbolic dynamics

resigning on numerical valuations at all

fair approximation for some systems

- famous symbolic types
  - cellular automata
  - L-systems

- cellular automaton
  - discrete system - linear, planar, etc.
  - state in the next step by a function on cell neighborhood
  - self-reproducible structures, game of life

- Lindenmayer systems
  - formal grammars, symbols and rewriting rules
  - used mainly for plant development modeling

Symbolic examples

- L-systems
  - algae: start A; rules $A \to AB$, $B \to A$
  - development:
    $n = 0$: A
    $n = 1$: AB
    $n = 2$: ABA
    $n = 3$: $ABAAB$
- Conway's game of life
  - infinite planar space of cells
  - eight neighbors for each cell
  - rules:
    live cell: 0 or 1 alive neighbors $\to$ dies
    live cell: 4 or more alive neighbors $\to$ dies
    live cell: 2 or 3 alive neighbors $\to$ lives
    dead cell: 3 alive neighbors $\to$ comes to life
    dead cell: otherwise $\to$ still dead

Stochastic dynamics

never is everything (deterministically) known

- changes
  - evolving processes
  - stationary processes
- differential equations
  - stochasticity inclusion (jumps, lags)
  - start conditions
- noise based order
  - continuous development into structure-less mediocrity
  - random jumps into border areas

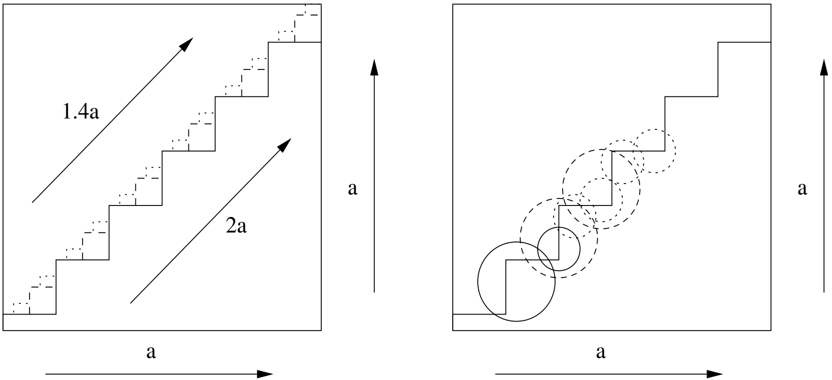
Probabilistic systems

- random walks
  - Brownian motion
    recurrence probability of 1 for 1D and 2D (discrete) spaces
  - blocked directions

- jump modes
  - uniform distribution
  - Lévy jumps
  - money circulation

- epidemic spread
  - based on Lévy jumps
  - continuous local spread
  - accidental further spread

- grain sensitivity
  - Boltzmann vs. Gibbs entropy
  - natural approximations



neuronal systems

another complexity stack on the life complexity stack

- system structure
  - ANN primarily a computation model
  - abstraction gaining system
  - connected areas accessible to specifications
- system development
  - network connecting and fixation
  - impulse based concept creation
  - a will to grasp

Tissues

- biochemistry
  - signalling cascades
  - coupled biochemical reactions
- differentiation
  - cellular surfaces
  - chromatin structures
- aberrations
  - pathological states
  - tumor development

Chromatin

the place of gene utilization

- states
  - specific DNA blocks (un)available
  - histone roles - weak for lower eukaryota
  - cell remodeling / differentiation
- 3D structure
  - DNA folding and accession for gene expression
  - modifications: DNA methylation, histone acetylation
  - regulation: signal cascades with phosphorylations

Evolution

- origin of life
  - RNA proto-world, ribozymes
  - code and genes sharing
- species
  - speciation: attractor changes
  - extinction: exponential process
- enzyme evolution
  - enzymes - receptors coevolution
  - Abzymes, i.e. antibody enzymes

Items to remember

Nota bene:

abstraction, orbits, stability

- dynamics
  - non-linear systems
  - qualitative description

- systems
  - symbolic, stochastic
  - composite, unique