System: any potential source of data
- boundary in vs. out
- inputs → environ infl. system
- outputs → system del. data

Experiment: Process of extracting data from a system
- observation of outputs
- perturbation of inputs & obtain of outputs

Model: A model of a system and a specific set of exp is anything to which the exp can be applied instead of the system
- experimental frame of a model
- a model is a system
- need not be mathematical

Simulation: experiment performed on a model
- within exp frame
- need not be computational

Modeling: Process of building a model.

Continuity Assumption

\[ \rho : \text{concentration} = \frac{\#}{V} \]
Knudsen number \( Kn \) : \( \frac{1}{\ell} \)

\( Kn \ll 1 \) → continuum if \( V > \lambda \)

\( Kn > 1 \) → always discrete!
Time Scales

- Models only contain a limited spectrum of time scales.
  - computational efficiency
  - numerical stability

\[
x(t) \quad \text{explicit Euler} \quad \frac{dx}{dt} = f(x)
\]

\[
x_{t+1} = x_t + hf'(x_t)
\]

\(t = 0, \ldots, T\)

want that \(x_{t+1} \approx x((t+1)h)\)

\[
\frac{dx}{dt} = -ax \quad \Rightarrow \quad x(t) = x_0 e^{-at}
\]

\(x_0 \quad x(t) \quad t\)

\[
* \quad x_{t+1} = x_t - ahx_t = x_t (1-ah)
\]

used: \(|1-ah| < 1\)

\[
L \quad 1-ah > 0 \quad \Rightarrow \quad 1 + ah < 1
\]

\[
h > 0
\]

\[
1-ah < 0 \quad \Rightarrow \quad -1 + ah < 1
\]

\[
ah < 2 \quad l < \frac{2}{a_{\text{max}}}
\]

\[
0 < h < \frac{2}{a_{\text{max}}}
\]
Distinguish:
- too slow  \rightarrow constant
- relevant  \rightarrow \text{dynamic eqs.} (ODE)
- too fast  \rightarrow \text{algebraic eqs.}

"Relevance" is defined by variables of interest & rep. frame of model.

FRAP ex.
relevant: diffusion of protein
          concentration field
slow: - room temp. changes
      - cell motion/deformation
fast:  - camera dynamics
        - laser switching dynamics

Reservoirs & Flows

Dynamics $\leftrightarrow$ Reservoirs/Storage/Integrators

for extensive quantities: ex:
- mass
- energy
- money
- information

$\Rightarrow$ Levels of reservoirs, called state var.

$\Rightarrow$ Flows between reservoirs.
Modeling Steps

1) Define system boundaries, inputs, outputs.

2) Identify reservoirs of relevant time scale and their levels. \[ \Rightarrow \text{reservoirs are independent.} \]

3) Formulate algebraic eqs. for flows between reservoirs.

\[
\text{Flow} = f(\text{activ. level} - \text{inhibit. level})
\]

4) Formulate balance eqs. for the reservoirs.

\[
\sum \frac{d}{dt}(\text{level}) = \sum \text{inflows} - \sum \text{outflows}
\]

5) Simplify eqs., recast algebraic parts, non-dimensionalize, normalize, ...

6) Solve model eqs. (analytically, numerically)

\[
\Rightarrow \text{level}(t) \quad \text{level}_t \bigg|_{t=0}
\]

7) Identify unknown parameters by fitting solution to data

8) Validate model using parameter values from (7) on data not used in (7).
Example: FLIP - experiment of ER lumen of living cell.

1) Boundary: ER membrane
   Inputs: bleaching
   Outputs: fluorescence

2) Fluorescence washes in ER lumen
   Too fast: fast & common
   Diffusion
   Too slow: changes in steady state
   Gene expression

3) \[ \frac{\partial m(t)}{\partial t} = \text{inflow} - \text{outflow} - \text{bleaching} \]

4) \[ \frac{dm(t)}{dt} = -\dot{m}_\text{out} = -\frac{V}{V}\beta(t-kat), \quad k = 0, 1, 2, \ldots \]

5) \[ m(t) = m_0 e^{-kt} \quad k = \frac{V}{V}\beta \]

6) \[ H(t) = \begin{cases} 0, & t < 0 \\ 1, & t \geq 0 \end{cases} \]

7) \[ k = \frac{V}{V}\beta \]

8) See slide.
Vector Calculus

1) Fields

- scalar fields: \( f : \mathbb{R}^n \rightarrow \mathbb{R} \) \((x) \rightarrow f(x)\)
  e.g. temperature, pressure, density, ...

- vector fields: \( \mathbf{v} : \mathbb{R}^n \rightarrow \mathbb{R}^m \) \((x) \rightarrow \mathbf{v}(x)\)
  e.g. force, electric field, director, ...

Field lines: curves \( \mathbf{x}(s) : s \rightarrow \mathbf{x}(s) \)
that is orthogonal to \( \mathbf{v} \) everywhere.

- stationary fields: value does not change over time

- unsteady fields: depend on time.

Derivatives of fields

\[
\frac{d}{dt}(a \cdot \mathbf{b}) = \frac{da}{dt} \cdot \mathbf{b} + \frac{db}{dt} \cdot a
\]

\[
\frac{d}{dt}(a \times \mathbf{b}) = \frac{da}{dt} \times \mathbf{b} + a \times \frac{db}{dt}
\]
2) Differential Operators

- Gradient $\nabla f(x)$

in Cartesian $\mathbb{R}^3$:

$$\nabla f(x) = \begin{pmatrix} \frac{df}{dx} \\ \frac{df}{dy} \\ \frac{df}{dz} \end{pmatrix}$$

$f(x) = f(x, y, z)$

in general:

$$\nabla f := \lim_{\nu \to 0} \frac{f(x + \nu) - f(x)}{\nu}$$

$f = f \Rightarrow \nabla f = 0$.

$\nabla f$ points the direction of steepest increase of $f$.

$\nabla f = 0 \Rightarrow$ extremum.

Isosurfaces $\nabla f = 0$.

Directional derivatives:

$$\frac{df}{dc} = c \cdot \nabla f$$

with $|c| = 1$. 
- Divergence \( \text{div} \, \mathbf{v} \)

In Cartesian \( \mathbb{R}^3 \):

\[
\text{div} \, \mathbf{v} (x, y, z) = \frac{\partial v_1}{\partial x} + \frac{\partial v_2}{\partial y} + \frac{\partial v_3}{\partial z}
\]

In general:

\[
\text{div} \, \mathbf{v} := \lim_{\Delta \to 0} \frac{\int_{\Delta} \mathbf{v} \cdot d\mathbf{s}}{\Delta}
\]

\[
\mathbf{v} = \mathbf{0} \quad \Rightarrow \quad \text{div} \, \mathbf{v} = 0
\]

\( \text{div} \, \mathbf{v} (x) \): source strength at \( x \).
\[ \text{curl } \mathbf{v} \]

in Cartesian \( \mathbb{R}^3 \):

\[ \text{curl } \mathbf{v} = \left( \frac{\partial v_z}{\partial y} - \frac{\partial v_y}{\partial z}, \frac{\partial v_x}{\partial z} - \frac{\partial v_z}{\partial x}, \frac{\partial v_y}{\partial x} - \frac{\partial v_x}{\partial y} \right) \]

in general

\[ \text{curl } \mathbf{v} := \lim_{\Delta \to 0} \frac{\int_{\Delta} \mathbf{v} \cdot d\mathbf{s}}{\Delta} \]

\[ \text{curl } \mathbf{v}(x) \text{: vortex strength at } x \text{. (vorticity)} \]
Laplace \( \Delta = \text{div} (\text{grad}) \)

\( \text{curl} (\text{grad}) \equiv 0 \)

\( \text{div} (\text{curl}) \equiv 0 \)

**Note:** Notation \( \nabla \)

in Cartesian \( \mathbb{R}^3 \):

\[ \mathbf{v} = \left( \frac{\partial v_x}{\partial x}, \frac{\partial v_y}{\partial y}, \frac{\partial v_z}{\partial z} \right) \]

\[ \text{grad} f = \nabla f = \left( \frac{\partial f}{\partial x}, \frac{\partial f}{\partial y}, \frac{\partial f}{\partial z} \right) \]

\[ \text{div} \mathbf{v} = \nabla \cdot \mathbf{v} \]

\[ \text{curl} \mathbf{v} = \nabla \times \mathbf{v} \quad (\text{rot}) \]

\[ \Delta = \nabla \cdot \nabla = \nabla^2 \]

3) **Flux** \( \Phi \)

\[ \Phi \]

If \( \mathbf{v} \) is a velocity field of a flow, how much fluid is transported through a surface \( S \) per unit time?

\[ \mathbf{v} \cdot \mathbf{n} \, dS \]

\[ \Phi = \int_S \mathbf{v} \cdot \mathbf{n} \, dS \]

\[ \Phi = \int_S \mathbf{v} \cdot \mathbf{dS} \]

\[ \Phi = \int_S \mathbf{v} \cdot \mathbf{dS} = \int_S \mathbf{v} \cdot ds \]
4) Work \( W \)

\[ \text{Q: if} \; \mathbf{v} \; \text{is a force field, how much work is done by moving a point mass along path } L \; \text{from } A \; \text{to } B. \]

\[ dW = \mathbf{v} \cdot d\mathbf{r} \]

\[ W = \int_{L} \mathbf{v} \cdot d\mathbf{r} \]
5) Integral Theorems

Gauss
\[ \oint_{\partial B} \mathbf{v} \cdot d\mathbf{S} = \iiint_B \text{div} \mathbf{v} \, dV \]
Net flow across \( \partial B \).

Stokes
\[ \int_C \mathbf{v} \cdot d\mathbf{r} = \int_{\partial S} \text{curl} \mathbf{v} \cdot d\mathbf{S} \]

Green: not elementary
\[ \text{Gauss: } \mathbf{v} = f \mathbf{r} \]
6) **Conservative Fields**

**Def.:** A vector field $\mathbf{V}(x, y, z)$ is called conservative if the work along all paths from $A$ to $B$ is same, for all $(A, B)$.

\[ W(L_1) = W(L_2) = W(L_3) \]

$\Rightarrow$ Work along any closed path is 0.

$\Rightarrow$ Work does not depend on path chosen, but only on start & end point.

$\Rightarrow$ $A$ & $B$ are state variables.

\[ \text{"friction/displacement-free"}. \]  \hspace{1cm} (\times)

7) **Differential Equations**

- Laplace \[ \Delta f = 0 \]
  \[ \text{div}(\text{grad}f) = 0 \]

- Poisson \[ \Delta f = g(x) \]

\[ (\times) \text{ fact: each gradient field is conservative and vice versa.} \]

If $\mathbf{V}$ is conservative, then

1. $\mathbf{f}$ s.t. $\mathbf{V} = \text{grad} \mathbf{f}$.
2. $\mathbf{f}$: potential

Each conservative field is vector whose

\[ \text{curl}(\text{grad}f) = 0 \]
Modeling Spatial Effects (Control Volume Concept)

Control Volumes

\[ x_1 < \text{control vol} < x_2 \]

Control Volume:
- Volume of integration
- Contained in a field
- Arbitrary shape & location

Euler:
- Fixed in space
- Flux of \( \mathbf{V} \) across boundary
- Material goes in & out

Lagrange:
- Move with velocity \( \mathbf{V} \)
- No flux of \( \mathbf{V} \) across boundary
- Always contains same material
Change

Field $f(x,t)$ e.g. temperature

What is change in $f$ that one measures in a control volume?

Euler

$$\left[ \frac{df}{dt} \right]_{x=\text{const}}$$

Field derivative

Lagrange

$$\frac{\partial}{\partial \tau} \left( f(x(t), \tau) \right) ; \quad \frac{dx}{dt} = v$$

$$= \frac{2f}{2x} \frac{2x}{2t} + \frac{2f}{2t}$$

velocity $v$

Lagrangian derivative

$$\frac{df}{dt} + \nabla f \cdot \mathbf{v} \mathbf{v} + \frac{Df}{Dt}$$

$$\frac{df}{dt} \quad \mathbf{v}$$

$$f(x,t)$$

$$\nabla f \cdot \mathbf{v} \quad \mathbf{v}$$

$$\nabla f = 0$$
Reynold's Transport Theorem (1875)

Extensive Lagrangian \[\leftrightarrow\] Intensive Eulerian
Reservoir levels \[\leftrightarrow\] Balance equations
Model \[\Rightarrow\] Simulate

How does an extensive quantity \( q = \int f \, dV \) change over time in a Lagrangian control volume?

For intensive quantities: \[
\frac{Df}{Dt} = \frac{\partial f}{\partial t} + \mathbf{v} \cdot \nabla f
\]

Conservation: An extensive quantity that is constant in a Lagrangian control volume is conserved.

\[
\frac{Dq}{Dt} = \frac{D}{Dt} \int_V f \, dV
\]

\[
= \int_V \left( \frac{\partial f}{\partial t} + \mathbf{v} \cdot \nabla f \right) \, dV + \int_V f \frac{D}{Dt} \left( \frac{dV}{dt} \right)
\]

\[
= \int_V \left[ \frac{\partial f}{\partial t} + \mathbf{v} \cdot \nabla f + f \mathbf{v} \cdot \frac{dV}{dt} \right] \, dV
\]

\[
= \int_V \left[ \frac{\partial f}{\partial t} + \mathbf{v} \cdot \nabla f + f \mathbf{v} \cdot \mathbf{v} \right] \, dV
\]

\[
= \int_V \left[ \frac{\partial f}{\partial t} + \mathbf{v} \cdot \mathbf{n} \right] \, dV
\]

\[
\frac{Dq}{Dt} = \int_V \left[ \frac{\partial f}{\partial t} + \mathbf{v} \cdot \mathbf{n} \right] \, dV = \frac{Df}{Dt}
\]

Balance equation
Chemical reaction model
Fluxes
Example: Diffusion

**Concentration:** \( c(x,t) \)

1) What quantity to model?
   - Mass \( m = \int_V u \, dv \)

2) Conservation law: assume conservation of mass

   \[ \frac{Dm}{Dt} = 0 \]

3) Apply Reynolds Transport Theorem

   \[ \frac{Dm}{Dt} = \int \left( \frac{\partial u}{\partial t} \right) \, dv + \int v \cdot (u \cdot n) \, ds = 0 \]

4) Algebraic equations for flows

   - Flux \( v^T u = -D \cdot u \cdot c \) (Fick’s law)

   - Diffusion constant \( D = \frac{c^2}{T} \)

5) Balance equations

   \[ \int \frac{\partial u}{\partial t} \, dv = -\int v \cdot (u \cdot n) \, ds = \int v^T (D \cdot u) \, dv \]

6) Simplify:

   \[ \int \left( \frac{\partial u}{\partial t} - D \cdot (D \cdot u) \right) \, dv = 0 \]

7) Go to arbitrary control volumes

   \[ \frac{\partial u}{\partial t} - D \cdot (D \cdot u) = 0 \]

   Diffusion equation

Assume: \( D(x, t) = D = \text{const} \)

\[ \frac{\partial u}{\partial t} = D \cdot u \]
Particle Methods for Spatiotemporal Simulation

- Function approximations
- Operator approximations

Modelling $\rightarrow$ Graph of injection reservoirs $\rightarrow$ PDE

Simulation

$u(x, t) \rightarrow \tilde{u}(x_p, t_j)$

$p = 1, \ldots, N$

$j = 1, \ldots, T$

$0 < |x_p - x_q| < \theta$

$\forall (q \neq p, p)$

finite diff. FEM TV Particle Methods

1) Particle = Lagrangian Control Volume
   Particle carry extensive quantities.
   $\Rightarrow$ close to the model.
2) in complex geometries,
   in moving geometries.
3) universal.
4) numerical stability, no CFL condition.

- boundaries are harder
- more costly
- need extra "tricks" (e.g. cell lists,
  remeshing, etc.)
Particle: \((x, c, u, v)_p; \quad p = 1, \ldots, N\)

Property: \(c_p = u_p \in (x_p, t)\)

Because: \(v_p \leq L^3; \quad \forall v_p = |x_p|\)

\[
\begin{cases}
\frac{dx_p}{dt} = \sum_{q=1}^{\infty} k(x_p, x_q, c_p, c_q) = u_p \\
\frac{dc_p}{dt} = \sum_{q=1}^{\infty} F(x_p, x_q, c_p, c_q)
\end{cases}
\]

\(K: \) ? evolution kernel

\(F: \) ? interaction kernel

Ex:

\[
\begin{align*}
\frac{du}{dt} &= f \\
\frac{u_n - u_{n-1}}{\Delta t} &= f_n \\
\text{discrete eqs.} &\Rightarrow \text{stability}
\end{align*}
\]

\[
U_n = U_{n-1} + \Delta t f_n
\]

\[
U_n = \sum \omega_k f_k
\]

\((1)\) intensive methods \(\Rightarrow f\)

\((2)\) extensive methods \(\Rightarrow \int f \, dt\)
Function approximation $u(x): \mathbb{R}^d \to \mathbb{R}$

Diffusion

Governing equation

$u(x,t)$: concentration

\[
\frac{\partial u}{\partial t} = \nabla \cdot (D(x,t) \nabla u)
\]

$D(x,t)$: Diffusion tensor

in Cartesian $\mathbb{R}^3$:

\[
D = \begin{pmatrix}
D_{xx} & D_{xy} & D_{xz} \\
D_{yx} & D_{yy} & D_{yz} \\
D_{zx} & D_{zy} & D_{zz}
\end{pmatrix}
\]

$D_{ij}$: diffusion coefficient for gradients in direction $i$ causing flux in dir. $j$.

- If $D(x,t) = D(x)$
  \[\Rightarrow\text{isotropic vs. anisotropic}\]
- $D$ is not a function of $x$.
  \[\Rightarrow\text{homogeneous vs. inhomogeneous}\]
- $D$ is not a function of $t$.
  \[\Rightarrow\text{normal vs. anomalous}\]

If isotropic & homogeneous & normal
\[
\frac{\partial u}{\partial t} = D \Delta u
\]
Anomalous Diffusion

below $\lambda$:

\[ \langle x^2(t) \rangle \propto DT \]

Brownian motion

\[ \langle x^2(t) \rangle \propto \alpha DT \]

\[ \alpha > 1 \]

\[ \Rightarrow \]

\[ 2\mu \frac{\partial n}{\partial t} = D \Delta n \]

\[ \alpha < 1 \]

\[ \Rightarrow \ t \]

\[ \langle x^2(t) \rangle \propto DT^\alpha \]

\[ \alpha \neq 1 \]

\[ \Rightarrow \text{anomalous diffusion} \]

\[ \langle x^2(t) \rangle \propto DT^\alpha = DT^{\alpha - 1} \]

\[ \frac{\partial \tilde{D}(t)}{\partial t} = \tilde{D}(t) \frac{1}{t} \]

\[ \alpha < 1 : \text{subdiffusion} \]

\[ \alpha = 1 : \text{diffusion / Brownian diffusion} \]

\[ \alpha > 1 : \text{superdiffusion} \]

\[ \text{Lévy flights} \]
Random Walk (RW)

\[ \frac{\partial u}{\partial t} = D \Delta u \quad \text{with} \quad u(x,0) = u_0(x) \]

Solution: Green's function

\[ u(x,t) = \int \frac{g(x,y,t)u_0(y)}{\sqrt{4\pi D t}} \, dy \]

Green's function:

\[ g(x,y,t) = \frac{1}{(4\pi D t)^{d/2}} e^{-\frac{|x-y|^2}{4Dt}} \]

Simulate Brownian motion of control volumes (\( \Rightarrow \)), then this is a numerical approx. of integral (\( \Rightarrow \))

\( \Rightarrow \) Monte Carlo integration
Particles: \( x_p(t), w_p = \psi\sigma(x_p) = \phi \)

\[
\begin{align*}
\frac{dx_p}{dt} &= \mathcal{N}(0,2D) + \mathbf{v} \\
\frac{dw_p}{dt} &= 0
\end{align*}
\]

Algorithm:

\text{Initialize:} \quad x_p(0) = \mathbf{v}\psi\sigma(x_p(0)) 

\text{Loop:} \quad d \sim \mathcal{N}(0,2D\Delta t) 
\quad x_p = x_p + d 
\quad t = t + \Delta t 

\text{End:} \quad \sigma = \frac{1}{2\pi \Delta x} \geq \sum_{p \in \mathcal{P}} \exp[-\|x_p\|^2] 

Choosing direction:

\( \theta \sim (0, \pi) \)

Step length: \( \sqrt{2D\Delta t} \)

\( \sqrt{2D\Delta t} \)

+)	 Easy to implement

+)	 Extends to more complex diffusions

+)	 Easy to include flows

-) Inaccurate error \( O(N^{-1/2}) \) for \( N \) particles.

-) Only works for "intermediate" \( D \) small \( D < \frac{2\Delta x}{\Delta t} \)

\[ \text{error} = \mathcal{K}D/\sqrt{N} \]

-) Complicated in bounded domains.

\( M \) triangles
\( N \) particles
\( O(MN) \)
Particle Strength Exchange (PSE)

\[ j = (m_2 - m_1) D \]

\[ \frac{dw}{dt} = \Sigma F(\ldots) \]

\[ \frac{du}{dt} = D \frac{\partial^2 u}{\partial x^2} \]

\[ n(y) = u(x) + (y-x) \frac{du}{dx} + \frac{1}{2} (y-x)^2 \frac{\partial^2 u}{\partial x^2} + \frac{1}{6} (y-x)^3 \frac{\partial^3 u}{\partial x^3} + \ldots \]

\[ \int_n \left( u(y) - u(x) \right) \frac{dE}{dE} (y-x) dy \]

Choose \[ n \] to be:
1. Even \[ \rightarrow \] all odd moments vanish
2. \[ M_2 \{ n \} = 2 \]
3. \[ M_i \{ n \} = 0 \]
\[ \forall \ z < i \leq r+1 \]

\[ \int_n \left( u(y) - u(x) \right) \frac{dE}{dE} (y-x) dy = \frac{D^2 u}{\partial x^2} \frac{\partial^2 E}{\partial x^2} + O(E^{r+2}) \]
\[ \frac{2\varepsilon^2}{\partial x^2} \int (y-x)^2 \eta (y-x) dy = \int (y-x)^2 \eta \left( \frac{y-x}{\varepsilon} \right) \frac{1}{\varepsilon} dy \]

\[ \eta \left( \frac{y-x}{\varepsilon} \right) = \frac{d\tilde{z} = \frac{1}{\varepsilon} dy}{\varepsilon^2 \tilde{z} \tilde{z}} \]

\[ \Rightarrow \int \varepsilon^2 \eta (z) d\tilde{z} = \varepsilon^2 \eta (\varepsilon z) \]

\[ \frac{\partial^2 u}{\partial x^2} = \frac{1}{\varepsilon^2} \left( \int (y-x) \eta (y-x) dy + o(\varepsilon^5) \right) \]

\[ \Rightarrow \frac{\partial^2 u}{\partial x^2} = \frac{1}{\varepsilon^2} \sum_{q=1}^{N} \lambda_q \frac{1}{\varepsilon} \int \eta (x) \eta (x_q - x_p) \]

\[ \lambda_q = \frac{\int \eta (x) \eta (x_q - x_p)}{q-1} \]

\[ \frac{dx_p}{dt} = \sqrt{\varepsilon} \sum_{q=1}^{N} \left( \frac{\partial u}{\partial x} \right) \eta (x_q - x_p) \]

\[ \frac{dx_q}{dt} = \frac{\sqrt{\varepsilon}}{2} \sum_{q=1}^{N} \left( \frac{\partial u}{\partial x} \right) \eta (x_q - x_p) \]

\[ F(x_1, x_2, c_{x_1}, c_{x_2}) = \frac{\varepsilon D}{2} \sum_{q=1}^{N} (x_q - c_{x_q}) \eta (x_q - c_{x_q}) \]

+ arbitrarily accurate
+ fast \( \Theta(N) \)
+ include flows
+ easy in complex geometrics
+ easy flow
+ find good \( \eta \)
+ boundary conditions are hard.