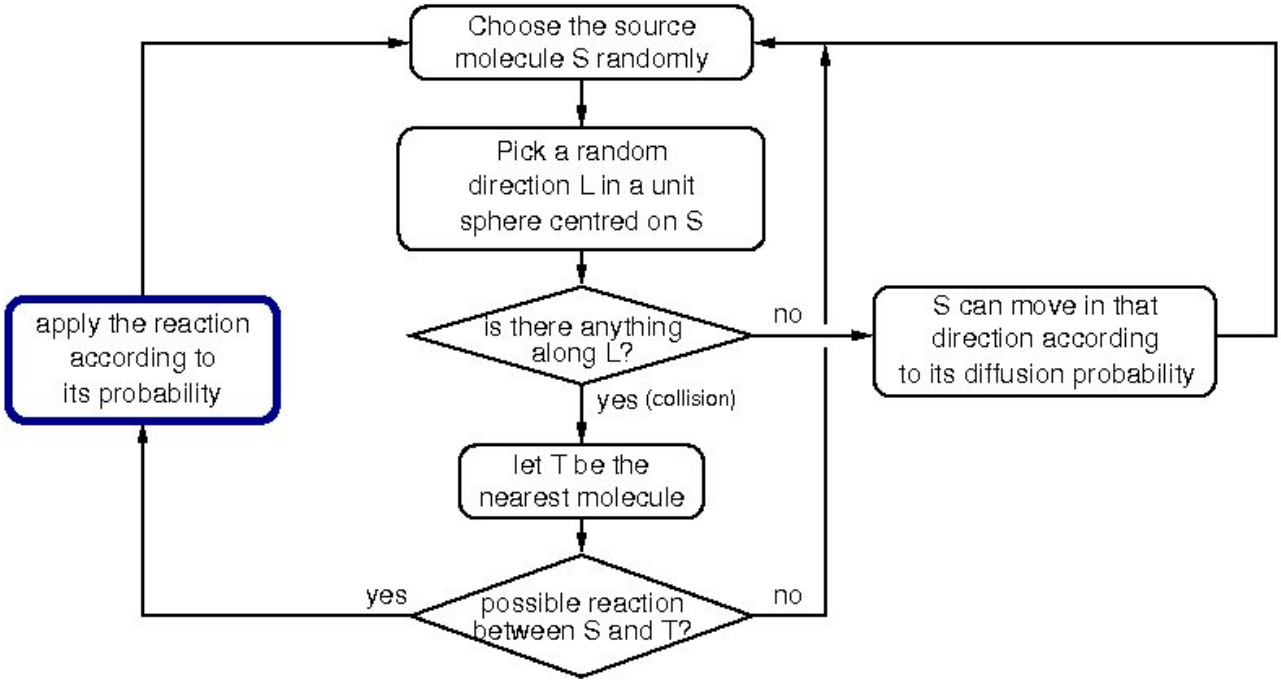
Overview

The simulator, HSIM, is a stochastic automaton driven by reaction rules between molecules.

In essence, each molecule is represented by a record that includes its type, its position, its size and a list of links to certain other molecules. HSIM keeps track of each molecule in real time from the computer point of view. The basic principle is that time is sliced into consecutive steps or generations, and in each generation the rules are applied to every molecule. These rules mimic the chemical reactions between molecules in a real system. The generation time is set to 100 microseconds, which corresponds to the average time for a protein to move a distance of 10 nanometers (of the order of its diameter) in vivo.

Metabolites diffuse faster than proteins, to take account of their smaller size, they are represented in HSIM by a sphere of reduced size with a greater diffusion speed. During a generation, the following processes are applied to all the molecules:

- the source molecule S is chosen at random (in order to avoid systematic artifacts);
- the presence of a target molecule, T, is checked for in close proximity to S by searching in a sphere of radius 10 nm centered on S along a random direction (two angles in the 3D space);
- if another molecule intersects this line and if a reaction rule exists between a molecule of type S and a molecule of type T, this rule is applied, according to a probability representing the reaction kinetics
- if not, molecule S may move to the empty location L, according to a probability representing the diffusion speed.



When all the molecules in the cell have been processed, the generation is completed and a new one begins. In HSIM the computer time is proportional to the total number of molecules and not to the size of the simulated space or the number of types of molecules.

One important point is that models in HSIM are *additive*: different models can be merged by simply merging their configuration files. If there are interactions between the models, HSIM will take them into account.

Rules

There are four kinds of interaction rules in HSIM between two molecules:

- **Reaction**: S reacts with T to produce two other types of molecules S' and T';
- **Association**: S binds to T to produce the complex S-T;
- **Dissociation**: the complex S-T dissociates into individual molecules S and T;
- **Catalysis**: the complex S-T is transformed into S'-T'.

Each rule has an associated probability which corresponds to the kinetics of the reaction. For each kind of

molecule, the maximum number of links to each other kind of molecule must be specified to allow the association rules to be functional.

Model Description

The model is described with a configuration file made of 5 sections:

- the size of the compartment and the *declaration* of each kind of molecules: the name of the species, the global maximum number of links to any kind of molecules, and if it is a membrane or a cytosolic molecule.
- the diffusion speed and the size of each kind of molecules.
- for each kind of molecules, the maximum number of potential links to each specific kind of molecule.
- the reaction rules.
- the initial population of each kind of molecules.

Example

```
title = "Enzymatic Reaction";

geometry = 120:40;    // 1.2 x 0.4 nm
molecule s1, s2;
molecule E1;

size (s1) = 0.1;
size (s2) = 0.1;
speed (E1) = 0.1;

maxlinks (E1) = s1(1), s2(1);
maxlinks (s1) = E1(1);
maxlinks (s2) = E1(1);

E1 + s1    -> E1 * s1   [0.4];    // E1 captures its substrate
E1 * s1    -> E1 + s1   [1e-3];   // reverse reaction
E1 * s1    -> E1 * s2   [0.01];   // catalyse s1 -> s2
E1 * s2    -> E1 + s2   [0.01];   // E1 releases the product

init (30, E1);
init (1000, s1);
```

Quick HSIM User Manual

Command line options

Usage: `hsim -f config-file [options]`

-h	print this help.
-H	longer help (with interactive controls).
-b file	batch mode (no OpenGL display).
-bd file	batch mode (without diffusion phase).
-C file	count each reaction and write it in 'file'.
-m num	set the duration of the simulation (number of seconds of simulated time).
-q	quiet (no display at all).
-v	prints the rules on stderr.
-r num	initialise the random number generator.
-ra	randomly initialise the random number generator.
-R	display the rules.
-fs	display in full screen mode.
-s	3D stereo mode.
-f file	use 'file' as configuration file.
-l file	load the simulation snapshot 'file' (infers the configuration).
-w	reload periodically the snapshot (watch file).
-g WxH	set the cell width and height.
-i num	set the number of generations between two histograms display.

-c MOL=num	add to the initial population of MOL 'num' more copies.

Keyboard controls

a	show all the molecules (even those not linked)
b	show the backbone of the assemblies
d	toggle diffusion only / diffusion and reaction
D	set the length of the simulation in seconds
g	toggle concentration curves / assemblies histogram
h, ?	show this help
i	save the current display in a PNG image file
l	load a previously saved simulation
m	start / stop recording a movie of the simulation
n	normalise the scale for displaying the concentration curves
+	increase the scale factor
-	decrease the scale factor
q, Escape	exit the program
r	show / hide the links between bound molecules
R	show / hide the rules
s	toggle the 3D stereoscopic mode switch
S	save the current state of the simulator into a file
Tab	start/stop the simulation
Return	toggle display rate
Backspace	focus to the center of the cell

Mouse controls

Left Drag	rotate around the X and Y axis
RIght Drag	change the aperture angle
Left Press	select a molecule to be the new center of rotation
Ctrl+Left Press	select an assembly to be shown
Mid Press	show a menu

Model description language

General syntax

title = "model name";	name of the model
speed (*mt*) = *prob*;	diffusion speed expressed as a probability
size (*mt*) = *num*;	diameter of a molecule type in 10 mn unit.
geometry = *lengh*:*diameter*;	size of the cell in 10 mn units.
display (mt_1, ..., mt_N);	show the concentration curves of the species list.
asm *name* = (mt_1, ..., mt_N);	give the name *name* to all the assemblies containing the species list.
maxlinks (mt) = mt_1 (nl_1), ..., mt_n (nl_n);	set the maximum number of links for species mt.
molecule $descr_1$, ..., $descr_n$	declare the species $descr_1$, ..., $descr_n$ as cytosolic molecules where $descr_i$ is 'mt [max link count] [hide] [inactive]'
membrane $descr_1$, ..., $descr_n$	declare the species $descr_1$, ..., $descr_n$ as membrane molecules
metabolite mt_1, ..., mt_n	declare the species as cytosolic molecules treated as an homogeneous population
init (#copies, mt);	fill the compartment with #copies copies of species mt.
init (conc uM, mt);	fill the compartment with conc micromolar of species mt.
init (conc mM, mt);	fill the compartment with conc millimolar of species mt.
surface (#copies, mt);	put #copies copies of the membrane species mt on one pole of the compartment membrane.

Syntax of the reaction rules

Basic reactions

mt_1 + mt_2 -> mt_3 + mt_4 [prob];	mt_1 reacts with mt_2 with probability prob;
mt_1 + mt_2 -> mt_3 * mt_4 [prob];	mt_1 reacts with mt_2 with probability prob and forms a complex where mt_1 become mt_3 and mt_2 become mt_4.
mt_1 * mt_2 -> mt_3 + mt_4 [prob];	the complex mt_1 / mt_2 dissociates with probability prob and mt_1 become mt_3 and mt_2 become mt_4.
mt_1 * mt_2 -> mt_3 * mt_4 [prob];	the complex mt_1 / mt_2 reacts with probability prob to transform mt_1 to mt_3 and mt_2 to mt_4.

Each molecule type of the left side of a rule can be more specific than simply the species name. The binding context can be expressed with this syntax:

mt	an instance of molecule type mt, bound or not to any other molecule
{mt_1}mt	an instance of molecule type mt which is already bound to a instance of molecule type mt_1
{~mt_1}mt	an instance of molecule type mt which is **not** bound to a instance of molecule type mt_1

Enzymatic reactions

A specific syntax has been implemented to model enzymatic reactions, allowing to specify the kinetics with the usual constants *Km* and *Kcat*, and units *µM* and *mM*. For example:

```
geometry = 60:60;
molecule   GOD;    // Glucose oxydase. Km = 30 mM, Kcat = 337
metabolite glucose, h2o2;

GOD (gluc -> h2o2) Km = 30 mM; Kcat = 337;
```

To implement this kind of reaction, HSIM use 3 standard rules and compute their probabilities to match the *Km* and *Kcat* values:

```
GOD   + gluc -> GODgl       [0.04884]
GODgl        -> GOD + gluc  [0.8]
GODgl        -> GOD + h2o2  [0.0674]
```