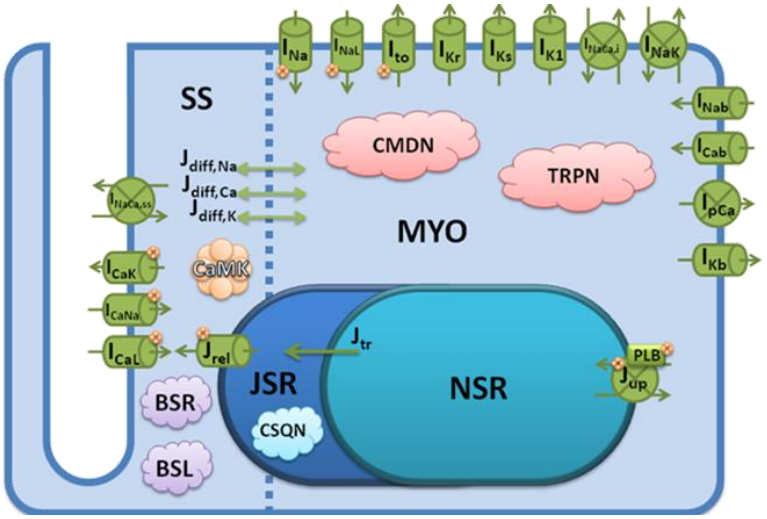
THE O'HARA-RUDY HUMAN VENTRICULAR AP MODEL

The O'Hara-Rudy (ORd) is the most updated human ventricular action potential (AP) model, based on data from more than 100 undiseased human hearts.
The structure is similar to the neuronal model developed by Hodgkin & Huxley in 1952, but with more state variables (41) and more ionic currents/pumps, and a more complicate intracellular compartmentalisation.
The Matlab/Octave file for the model consists of a function file **modORd_endo.m**, which takes as input the time (**t**) and the state variable vector (**X**), and gives as output the derivative of the state variables in time (**dX**).



The function is called by the **MainFile_modORd.m** which solves the model by using the built-in Matlab/Octave function *ode15s*, particularly suitable for stiff problems.

REF: http://journals.plos.org/ploscompbiol/article?id=10.1371/journal.pcbi.1002061

EXERCISE 0: THE O'HARA-RUDY MODEL

Have a quick look at the Matlab/Octave files provided, to understand their structure. Simulate the O'Hara-Rudy model by running the *MainFile_modORd.m*, and visualise the membrane voltage and the ionic currents.

Two AP biomarkers are also computed:

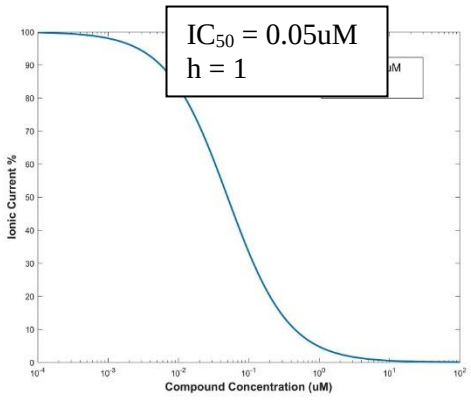
- $APD_{90\%}$: used to measure the length of the AP
- dV/dt_{MAX} or upstroke velocity: used to measure how fast the AP reaches the peak

SAFETY PHARMACOLOGY

Computational models can be used to predict in simulation the effect of specific drugs on cell electrophysiology. Usually, a single compound affects one or more ionic currents, decreasing them. These changes can be estimated by a sigmoidal dose-response curve, based on the experimental data available.

Each curve is characterised by 2 parameters:

- **IC_{50}**, i.e. the concentration which reduces the current by 50%
- Hill Coefficient (**h**), which is related to the slope of the curve



$$I_{\%}(X) = \frac{100}{1+(\frac{X}{IC_{50}})^{h}}\%$$

where $I_{\%}$ is the percentage of the ionic current remaining after the addition of the concentration X.

For the purpose of this exercise, we will focus on 3 ion channels: I_{Na}, I_K, and I_{Ca}.

Each of these will have their own IC_{50} and h, specific for each drug.

EXERCISE 1: IN SILICO DRUG TRIALS

Investigate the effect of the 4 different drugs listed below in the ORd model, by including the drug information (IC_{50} and h) in the *MainFile_ORd.m* (lines 31-59).

Drug Name and Class	Effect on INa	Effect on IK	Effect on ICa
Lidocaine (Class I)	IC_{50} = 3 µM and h = 1	*No Effect**	*No Effect**
Dofetilide (Class III)	*No Effect**	IC_{50} = 3 µM and h = 1	*No Effect**
Diltiazem (Class IV)	*No Effect**	*No Effect**	IC_{50} = 3 µM and h = 1
Flecainide (Class I/III)	IC_{50} = 3 µM and h = 1	*No Effect**	IC_{50} = 3 µM and h = 1

*For *No Effect* please consider IC_{50} = 1 µM and h = 0

Test multiple concentrations for each drug to see how the effects vary with the dose:

- Suggested range: 1, 10, 100, 1000 µM

These are all anti-arrhythmic drugs, usually used to treat cardiac arrhythmias. They are classified in difference classes, depending on which cardiac ion channel they affect the most. In some cases, anti-arrhythmic drugs can cause cardiac side effects, like the ones mentioned in the slides.

Which biomarker changes can you see for each drug? Do you see any abnormal drug-induced phenotype in repolarisation or depolarisation? Which drugs would you classify as risky?

Send your answers on Slido!

Tip: You could write a for cycle to change the concentrations and show all the corresponding APs in the same figure. Open one of the *Exercise1_solution* to see how this can be done using Octave.

EXERCISE 2: MODELLING HEART FAILURE (OPTIONAL)

Drug-induced arrhythmias are rare events, and they usually do not happen in healthy people. Patients that have some cardiac conditions might be more likely to develop adverse drug reactions.

Build a human AP model of heart failure, by scaling some parameters of the ORd model based on the Table here below:

Parameter	Scaling Factor
GNaL	1.5
PCa	1.5
Gncx	1.5
PnaK	0.5
GKr	0.5
GKs	0.5

Hint: Duplicate modORd.m to create a new function file modORd_HF.m with modified parameters.

Now you can repeat the drug testing from EXERCISE 1 using *modORd_HF.m* instead of *modORd.m*.

Are the drug effects different? How does the risk prediction change?

N.B. If you do not have time to test all drugs, you can look at the solution files. They are available for all drugs, and for both modORd or modORd_HF.