

Ronald: A Domain-Specific Language to study the interactions between malaria infections and drug treatments

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Abstract *Malaria kills more than 1 million people a year, mostly children in sub-Saharan Africa. Antimalarial drug resistance is one of the greatest challenges facing malaria control today. We present Ronald, a Domain-Specific Language to model the fundamental forces driving antimalarial drug resistance including drug pharmacokinetics and pharmacodynamics, drug regimens and parasite genotypes. Example of applications of this language include the study of the consequences of counterfeit or lower quality drugs, the implications of different dosage regimens, the impact of drug half life on the emerging and spread of resistance and the benefits and drawbacks of combination therapies, among many others.*

Keywords: malaria, domain specific languages, bioinformatics, infectious diseases, pharmacology

1 Introduction

P. falciparum malaria is the most important parasitic disease of humans, causing more than 1 million deaths, mostly in sub-Saharan Africa. This heavy death toll is held in check by the availability of cheap and effective antimalarial drugs. The malaria parasite, however, has evolved mechanisms of resistance to many of the available antimalarials, and morbidity and mortality rise as efficacy falls. In this context understanding the mechanisms of resistance and their consequences is fundamental in shaping effective public health policies against malaria. Many of currently existing studies about resistance are theoretical in nature (e.g. [1, 2, 3]) and would benefit from computational models for their comparison and assessment.

Domain-Specific languages (DSLs) are programming languages tailored to a certain application

domain, they are more expressive and easier to use than general purpose programming languages when applied to problems to which they were constructed[4]. Code written in a DSL is normally more compact, thus increasing productivity and can easily be shown to and discussed with domain specialists (in our case, MDs, epidemiologists and population geneticists).

Here we present Ronald, a DSL to model the interactions between malarial parasite infections and drug treatments. Our approach concentrates on creating a clear, expressive and declarative specification that can be understood by domain specialists and in separating language specification from behaviour. This means that a single specification can be used for many tasks from scenario analysis to documentation and graphic production to generation of code in a general purpose language for simulation. Ronald already has some practical applications which will be presented and discussed.

2 Concepts

The DSL allows us to model the fundamental concepts involved in the interaction between drugs and parasites. Those concepts are presented in this section.

2.1 Parasites

Parasite resistance is achieved by mutations in key enzymes with which drugs interact. As an example the drug SP (Sulfadoxine-Pyrimethamine), available under the commercial name Fansidar®, inhibits the folate production pathway of the parasite[5]. SP, inhibits both the usage of external folate (through inhibition of the enzyme dihydrofo-

late reductase – DHFR – mainly by Pyrimethamine) and *de novo* folate production (inhibition of dihydropteroate synthase – DHPS – by Sulfadoxine). Parasite resistance to SP is attained by mutations on both genes that code the enzyme. Drug resistance with SP is not a “black and white” process: an increasing number of successful mutations in the parasite make it less and less sensitive to the drug. Furthermore as the parasite usage of external folate is more important than “de novo” creation, mutations on DHPS are only relevant if DHFR is already resistant.

In this context a DSL needs the ability to express the notions of mutation, especially at the protein level. To code for the necessary mutations for DHFR the following could be done:

```
DHFR = protein("DHFR")
DHFR.mutatingAmino 51, Asn, Ile
DHFR.mutatingAmino 59, Cys, Arg
DHFR.mutatingAmino 108, Asp, Asn
```

There are three mutations, the first being at position 51, where the wild type is an Asparagine and the mutant an Isoleucine. Nothing is said about the relative importance of these mutations as that is coded on the pharmacodynamic description of a compound.

2.2 Drugs and Compounds

The word “Drug” is used in the literature with two different meanings: as referring to a unit of prescription taken and also referring to an active compound. For clarity and precision we will use the word “Drug” in the former sense and the word “Compound” for the latter. As such, the drug SP has two compounds, Sulfadoxine and Pyrimethamine. In cases where a drug has only a single compound, then the name may overlap (as in the case of Chloroquine). An initial modeling of SP could be:

```
sulfa = compound(
  name      : "Sulfadoxine"
  abbreviation : "S",
  halfLife  : 116.h
)

pyre = compound(
  name      : "Pyrimethamine",
  abbreviation : "P",
  halfLife  : 83.h
)
```

```
SP = drug("SP")
SP.includes sulfa, 500.mg, 408
SP.includes pyre, 25.mg, 34
```

An SP pill has two compounds, Sulfadoxine with 500mg with a bioavailability coefficient (explained below) of 408 and Pyrimethamine. Each compound has a default half life. Time, mass and concentration units have their own mini-languages, as these are used frequently (e.g. to specific compound concentrations in the blood or compound dosages) allowing the user to specify quantities in any unit deemed appropriate instead of a pre-defined unit (e.g. sulfadoxine half life is 116.h instead of 6960 if the canonical unit was minutes), not only can the specification be done in the most natural unit (e.g. hours or days for sulfadoxine half life but minutes for artesunates) but also conversion between units is completely automated.

2.3 Pharmacokinetics

Most malarial drugs are taken orally, so a complete pharmacokinetical (PK) model is necessary (i.e. including absorption in addition to its subsequent distribution around, and elimination from the body).

The language allows for the user to choose among existing PK models which can be extended. For instance, the calculation of the fundamental Area Under the Curve (AUC - the curve being the concentration of the compound over time) parameter will be strongly impacted by absorption rates in short lived compounds like artesunates whereas for long lived compounds an absorption model with bioavailability alone normally suffices. Currently linear absorption rates can be modeled and the user can extend the system to support more absorption models. For elimination, single and multiple compartmental models are available.

Regarding the example above, elimination is modeled by a single compartmental model with a certain half-life and both absorption and distribution are modeled via a bioavailability coefficient which converts drug dosage in mg/kg to plasma drug concentrations. This simple model covers all the modeling efforts in malaria drug resistance known to us, but we expect that, when studying artesunates or SP efficacy in children[6] more refined absorption and distribution models will be needed.

2.4 Effects (pharmacodynamics)

A compound is able to kill a certain proportion of parasites over time, that effect is normally called the

pharmacodynamics (PD) of a drug.

A change in parasitemia can be described by

$$dP/dt = aP - f(C_{c1}, \dots, C_{cn})P - g(I)P$$

Where a is the growth rate of the parasite, f is a function representing compound killing effects and g is a function of host immunity.

Here we are concerned with f only, which is the PD function. As an example, for mefloquine[3] the following formula can be used:

$$f(C) = k_1 \frac{MQ^\gamma}{MQ^\gamma + IC_{50}^\gamma}$$

Where k_1 is the first order parasite killing rate corresponding to 3.45/day, MQ the current mefloquine concentration, IC_{50} the drug concentration that kills 50% of parasites estimated to be 665.4 μ g/ml and γ is the slope of the concentration-effect curve estimated at 2.44.

Modeling this in Ronald is done in the following way:

```
effect = effect(  
  name      : "General effect",  
  formula   :  
    { 3.45 * MQ**y / (MQ**y + IC50**y)},  
  parameters :  
    [IC50 : 665.4.microg / ml, y : 2.44]  
)
```

IC_{50} and γ in this example are parameters for the mefloquine sensitive parasite.

We now present a more complex example: the effect of SP (a drug with two compounds) on both drug sensitive and drug resistant DHFR parasites. DHFR resistance meaning parasites can still use exogenous folate even in the presence of a drug that inhibits its use. We will use an “all or nothing” model where when the compound concentrations drops below a certain threshold there is no effect, and when above the whole infection is cleared.

```
exogenous = effect(  
  name :  
    "Exogenous folate usage",  
  formula : {  
    if (sConst * min(sulfa, 5000) +  
        pyre - pLim > 0)  
      return infinity  
    else  
      return 0  
  },  
  parameters :  
    [sConst : 0.14, pLim : 2.7]
```

```
)  
  
exoRes = resistance(  
  effect      : exogenous,  
  mutations   : [DHFR.mutation 108],  
  parameters  : [sConst : 0.14, pLim : 2000]  
)
```

The threshold formula is obtained from interpreting the isobolograms in [7]. Here an *if* construct of the host language is used and a resistance element, dependent on a mutation on codon 108 of DHFR, is introduced. Different levels of resistance have different parameters for the equation threshold, in this case, the pLim parameter related to Pyrimethamine concentration increases by three orders of magnitude.

Ronald also allows preferences between effects, for instance to specify that “de novo” folate creation effect should only be used if the parasite is resistant with regards to exogenous folate usage.

2.5 Drug Regimens

The DSL supports specifying drug regimens, for example:

```
SPregimen = regimen()  
SPregimen.take 3.pills, of: SP, at: 0.h  
SPregimen.take 3.pills, of: SP, at: 1.d
```

In this case a new regimen is created, where 3 SP pills are given at the beginning and again one day after. Being able to specify regimens is important to study resistance spread as it is expected that non-compliance, especially with Artemesinin Combination Therapies which requires adherence to a drug regimen for up to three days, might drive the spread of resistant forms[8].

3 Architecture and implementation

Ronald is embedded in an host language, meaning that the full power of a general purpose language is still available in case of need. The host language is Groovy (with an initial prototype made in Scala) which has many facilities to support DSLs, being a Java Virtual Machine (JVM) based language means that all JVM/Java based libraries are available for use. An initial implementation, which is able to handle most of the applications presented below, is available at <http://popgen.eu/ronald>.

The architecture is depicted in figure 1. A DSL processor is able to handle programs irrespective of the possible uses. What is done with a specification depends on the backend, we currently support three different backends:

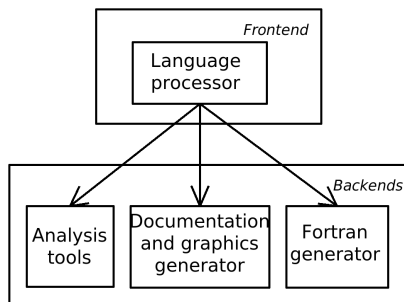


Figure 1: Ronald architecture

1. A Fortran generator that takes the program specification and generates code to change the simulator described in [9]. This generator is able to change existing simulator code by adding new drugs to be used in an environment where many other factors are included (vaccination, within-host dynamics, mosquito transmission, ...). This expands the scope of usage for Ronald by several orders of magnitude as this simulator incorporates many other factors besides the relationship between drugs and parasites.
2. A documentation and graphics generator that translates the specification to readable English in \LaTeX format. The generator is also able to create graphics like pharmacokinetical profiles for drug regimens or isobolograms for the 50% inhibition (IC_{50}) of parasite replication *in vitro* from PK profiles
3. Internal analysis tools are provided, for instance given a simple “all or nothing” PK model presented above, the system is able to calculate how many days after treatment drugs remain effective against a certain parasite strain before they decay to ineffective concentrations.

4 Applications

Ronald can help answer many questions. Here we present a few examples of problems that can be addressed.

Pharmacokinetical profiles of drug regimens can be computed and plotted, a standard Coartem® regimen of 6 doses over 3 days is presented in figure 2 (The figure is a direct output from the graphic generator with no post-processing or edition).

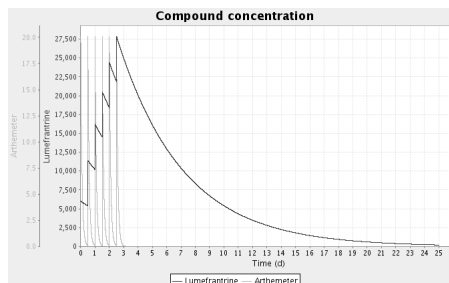


Figure 2: Pharmacokinetical profile of a typical Coartem® regimen

A fundamental variable for the spread of drug resistance is the window of time following treatment where a drug is present at concentrations sufficiently high to be effective against a sensitive strain but not against a more resistant one. The system is able to estimate, given a PK/PD profile, the estimated time for which a drug is effective against a certain malaria strain. An example that can perform this calculation is made available on the web site.

Another problem occurring in places where malaria is prevalent is the usage of low quality or counterfeit drugs. Low quality drugs normally have less bioavailability than better ones, which has an impact on cure rates, either because the dosage available is not able to cure more resistant strains or because the time during which the drug has efficacy is reduced. This increases the spread of more resistant forms of the parasite. The system is able to simulate this scenario in a succinct and elegant way: A simple bioavailability study requires only creating a new drug with a different bioavailability coefficient, normally an exercise taking literally half a dozen lines of code.

We are currently studying the impact of longer chloroquine regimens, as used in Guinea-Bissau[10] on the spread of chloroquine resistance. There is interesting empirical[11] and theoretical[12] evidence that changing Chloroquine regimens might have a positive impact on cure rates and resistance spread. This study is made by generating Fortran code that is integrated on the simulator introduced above, allowing for a population simulation where spread can be tracked and studied.

5 Discussion and future work

The initial version of Ronald is already able to answer interesting research questions while allowing productivity gains on the production of code. Most importantly, it is possible to write code in a format that is declarative enough to be discussed with domain experts. There are still many issues to be resolved and expanded, the most important are presented here:

Although most drug resistance mechanisms are related to enzyme mutations, at least some (e.g. Mefloquine) seem to be related with copy number variation[13]; the same mechanism might also apply to Artesunates. We plan to support modeling copy number variation in the future.

We would like to support as many PK and PD models as possible. The quality of information existing in the literature varies substantially from drug to drug, making some models more applicable than others depending on the drug.

A DSL makes cooperation between programmers and domain specialists much easier, but it is not realistic to assume that most domain specialists will start writing DSL code. The creation of user interfaces on top of Ronald might be done in the future. A possible strategy might be the partial automated creation of UIs from the language specification.

Currently there is no support to model different human properties as we rely on the external Fortran simulator to deal with humans. A more expressive and realistic DSL will require modeling at least of age and weight, factors which clearly influence drug effectiveness. To a lesser extent supporting the modeling of infection growth might also be necessary in the future.

The fundamental issue is dealing with the inherent fuzziness and uncertainty of the dependencies of certain system properties. As an example, in Ronald bioavailability is dependent only on the drug. In reality compound bioavailability is dependent on many factors like age[14] or diet[15], as well as on drug quality. Most factors might be unknown and vary from drug to drug. A similar reasoning can be applied to compound half life. The most obvious solution is to redesign the language in order to allow as much flexibility as possible. But, in many cases, simple models are sufficient and DSL users shouldn't have to parametrize the more complex model just to obtain results that could be obtained with a simpler model. That would cause lost productivity and expressiveness. There is a challenge in designing a language that can accommodate all the uncertainty

in modeling complex and partially unknown natural processes while maintaining conciseness in cases where simpler models of reality are acceptable. We argue that the approach outlined above has the potential to achieve this.

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