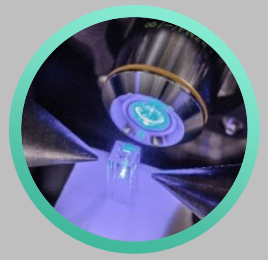
Merlin – Your Electronic Laboratory Assistant

Sebastian Schoening, Franziska Maugg
Fraunhofer Project Group for Automation in Medicine and Biotechnology

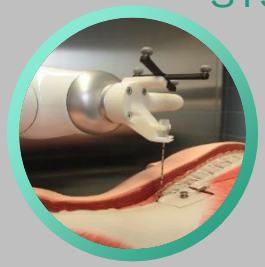
Berlin, March 15th, 2015

FRAUNHOFER PAMB WHO ARE WE?

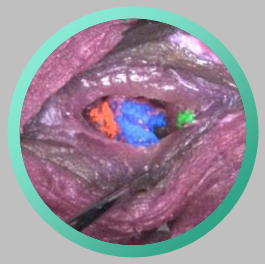
INFORMATION SYSTEMS



BIOPROCCESS ENGINEERING



CONTROL SYSTEMS



BIOMEDICAL OPTICS

MICRO-MECHATRONICAL SYSTEMS

- Fraunhofer “Project Group for Automation in Medicine and Biotechnology” (PAMB)
- Established in July, 2011
- Approx. 45 scientific employees (+ 70 students)
- Located at the University Medical Centre Mannheim
- Cooperation with Medical Faculty in Mannheim of the Heidelberg University
- Parent Institute: Fraunhofer Institute for Mechanical Engineering and Automation (IPA), Stuttgart

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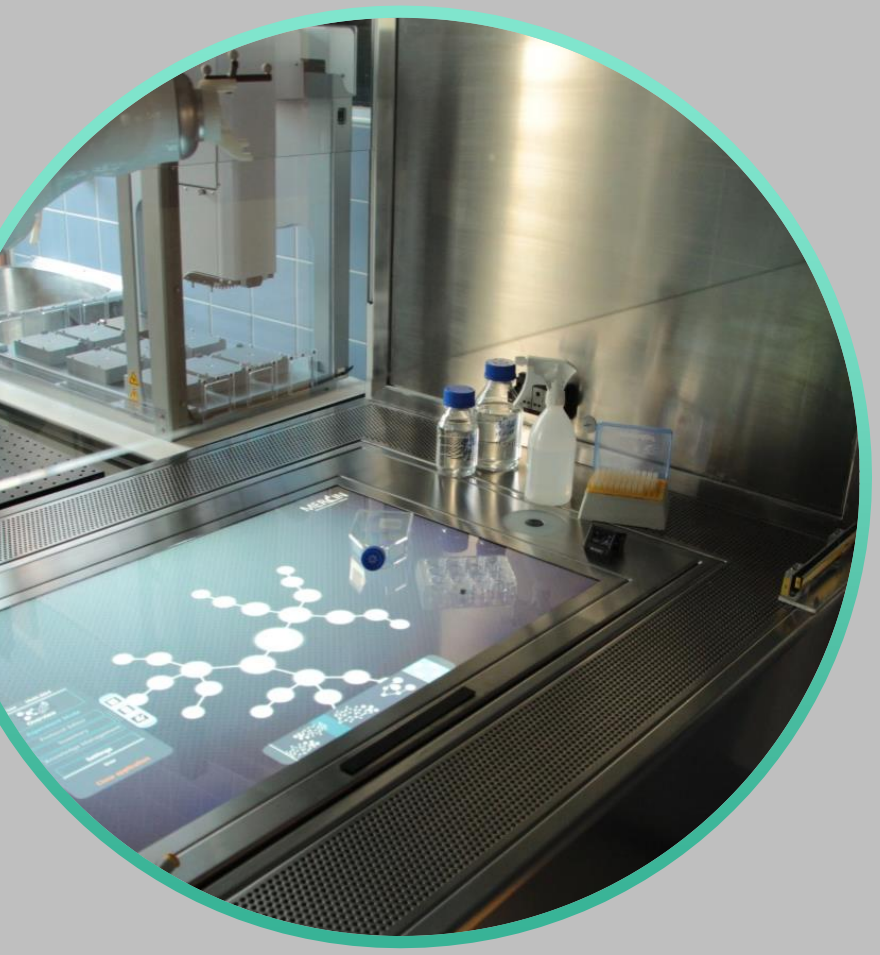
What we are not talking about today?

WHERE DID WE COME FROM?

EARLIER PROJECTS MERLIN MANUCYTE



- Multi-touch displays embedded into lab benches
  - Workplaces become computer interfaces
  - Basis: dedicated electronic lab notebook software called Merlin
  - Hybrid work fashion: intertwining automated and manual workflows
  - Consistent documentation
  - Interfaces to external data and knowledge management systems
  - Ongoing project, visit our lab!

MERLIN BENCH

USER INTERACTION FOR STERILE ENVIRONMENTS

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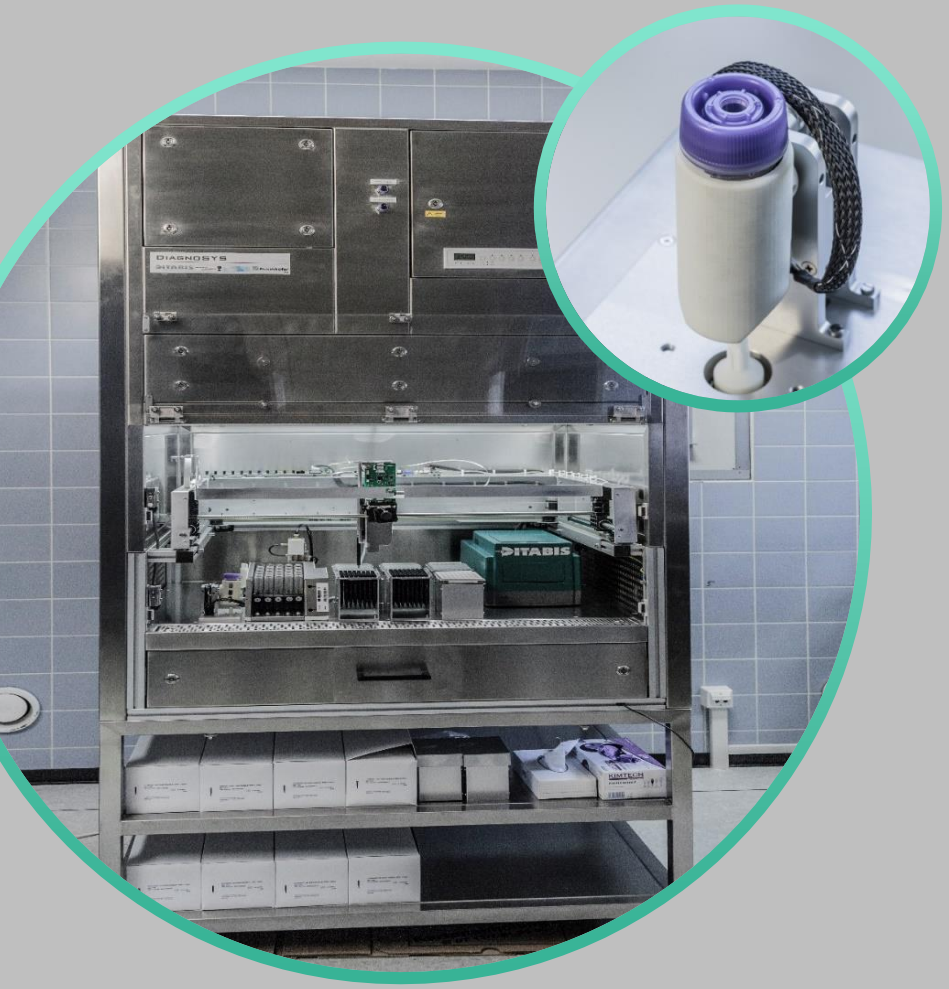
PROCESS COGNITION
PROJECT DIAGNOSIS (HARDWARE)



- Platform for personalized diagnostics
  - analysis of chemo-sensitivity of mamma and ovarian carcinoma (sterility level S2)
  - automated single-cell generation from biopsies
  - isolation of tumor cells my means of application of magnetic bead technology
  - results are measured based on ATP luminosity and uPA / PAI-1 ELISA
- development of small-size lab-bench devices for single-cell solutions from cell suspension for automated and manual handling

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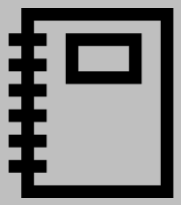
What we are talking about today!

PROCESS-CENTRIC MANAGEMENT OF LABORATORY WORK

RECAP LABORATORY NOTEBOOK CLASSES

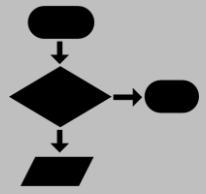


paper-based

word processor
& spread sheets

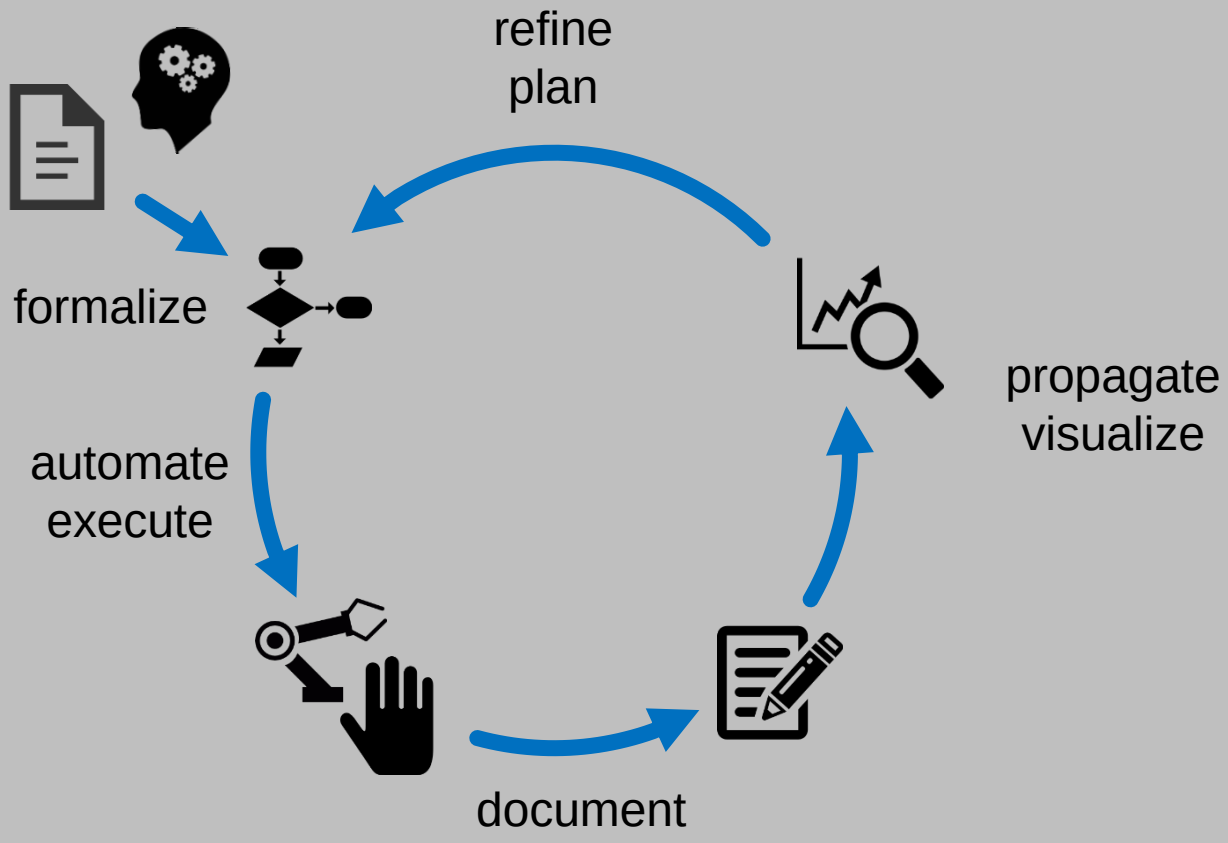
database-
driven
(SQL)

document-
driven
(noSQL)

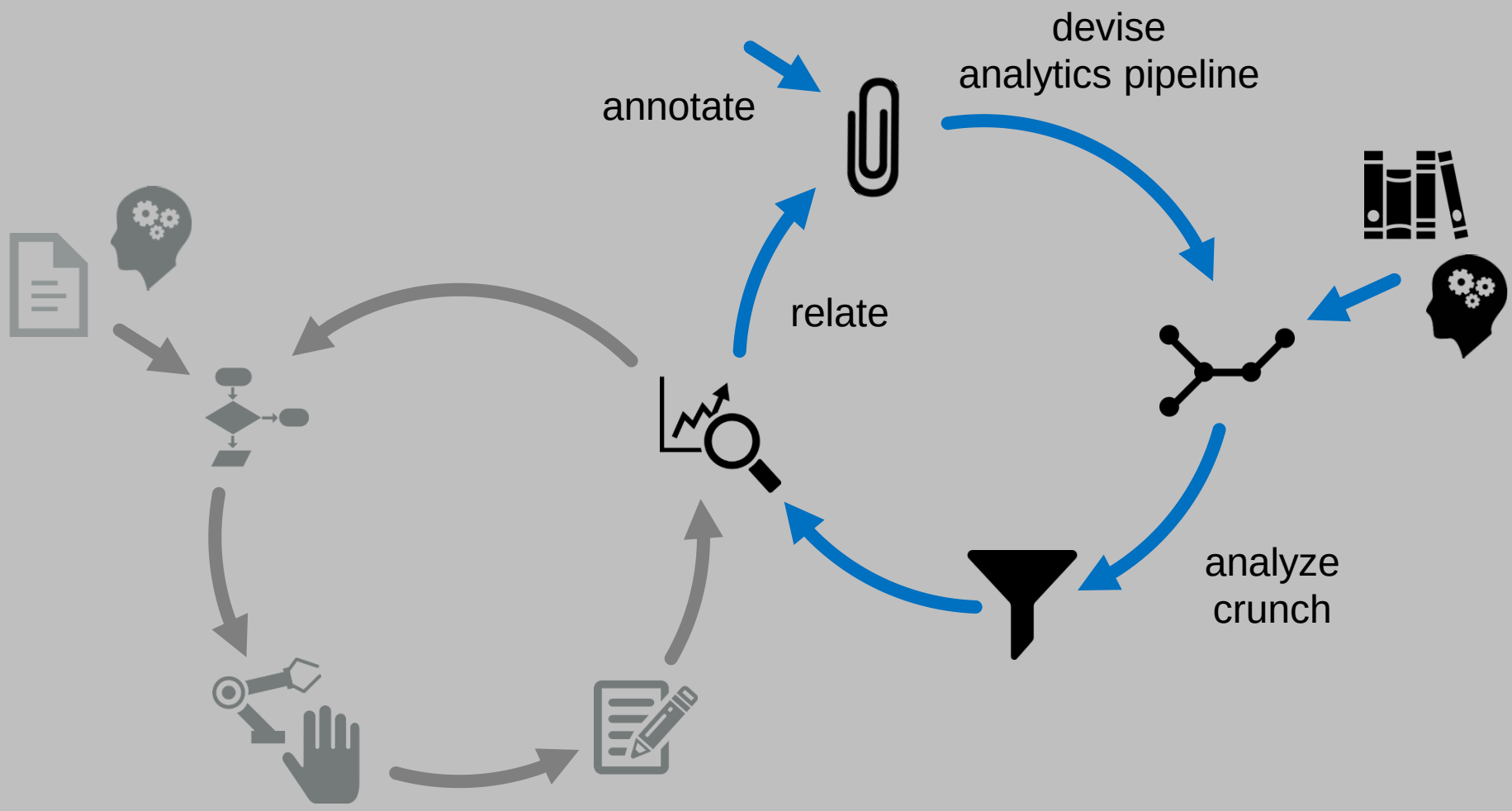


process-
driven

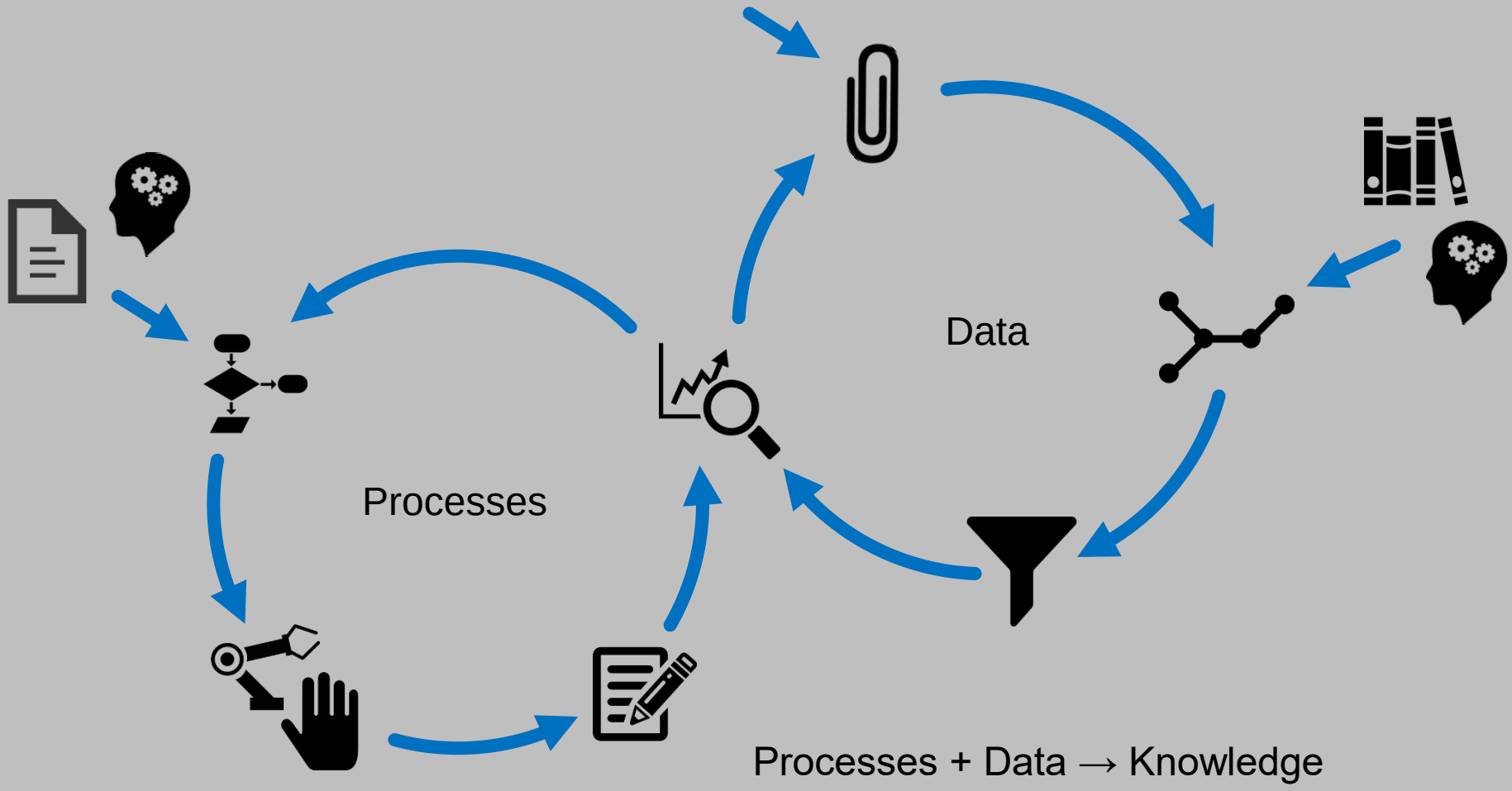
EXPERIMENTATION PROCESS PERSPECTIVE



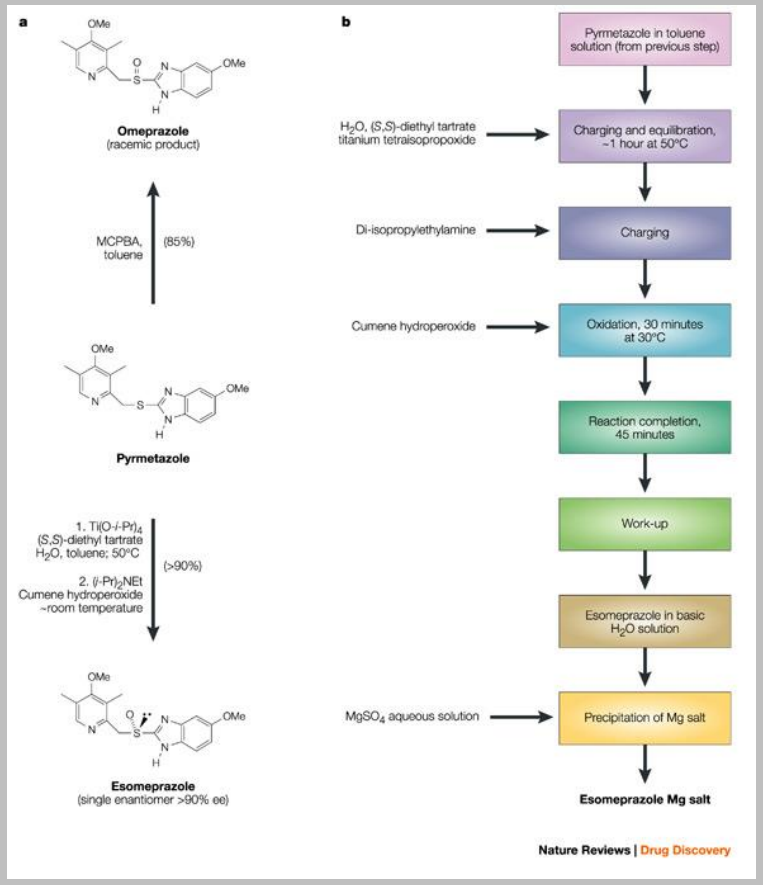
EXPERIMENTATION DATA PERSPECTIVE



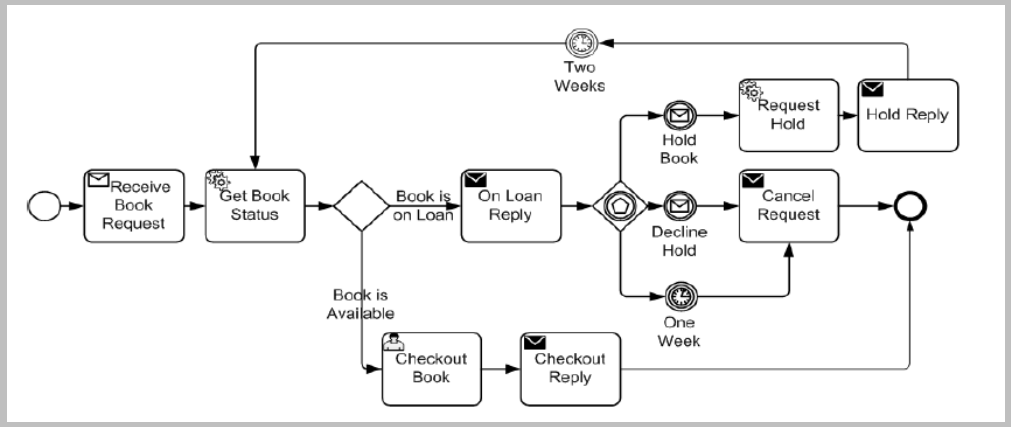
EXPERIMENTATION PROCESS PERSPECTIVE



PROCESS DESCRIPTION REPRESENTATIONS



Flow Chart, http://www.nature.com/nrd/journal/v2/n8/fig_tab/nrd1154_F8.html



BPMN-Chart, http://www.brsilver.com/wp-content/uploads/library_spec.png

	Hauptschritte	Schritte	Beschreibung	Volumen	Puffer	Temperatur	Wählbar
0	Lagerung im Automaten (manueller Eintrag)	Puffer	- Bindungspuffer BB - 10fach Bindungspuffer - spezieller Wasch-/Blockierungspuffer zur Vorbehandlung der Neg- bzw. TargetBeads (z.B. mit Herring Sperm DNA) (optional) - spezieller Waschpuffer für Target-SELEX (optional) - spezieller Elutionspuffer für Negativ- bzw. Target-SELEX (optional) - PCR-Mastermix - Puffer NT aus MN-Kit - Puffer NTC aus MN-Kit - Puffer NT3 aus MN-Kit - Puffer NE aus MN-Kit - 10fach λ-Exonuclease-Reaktionspuffer - λ-Exonuclease-Enzymlösung - reinst Wasser ???	~3000µl + 1200 ~20µl ~400µl min. 200µl ~250µl 80µl + 80µl K 400µl 400µl 720µl 560µl 20µl 2µl		RT RT KS ? RT RT KS ? RT RT RT RT RT KS !	- Bindungspuffer-Variante für jeden SELEX einstellbar - zur entsprechenden Bindungspuffer-Variante - wählbar ja/nein und welcher - wählbar ja/nein und welcher - wählbar ja/nein und welcher - evtl. verschied. Varianten je SELEX
0	Lagerung im Automaten (manueller Eintrag)	NegBeads - Stammlösg.	- Beadlösung mit eingestellter Beadzahl/ml (1x 10⁸ Beads/200µl = 5x 10⁸ Beads/ml)	200µl	in BB	KS	- verschied. NegBeads je SELEX
		TargetBeads - Stammlösg.	- Beadlösung mit eingestellter Beadzahl/ml (1x 10⁸ Beads/200µl = 5x 10⁸ Beads/ml)	200µl	in BB	KS	- verschied. TargetBeads je SELEX
		SELEX - Bibliothek (nur für Runde 1)	eingestellte Konz.: 2.5nmol/200µl in BB = 12.5µM 2x 100µl/well in PCR-Platte vorlegen	2x 100µl	in BB	KS ?	- verschied. Bibliotheken je SELEX
		ssDNA(SFI) als Ausgangslösung für Eichkurve: 100pmol/ml in BB	eingestellte Konz.: 100pmol/ml in BB	200-300µl	in BB	KS ?	- verschied. Ausgangslösungen je nach verwendeter SELEX-Bibliothek bzw. je nach verwendeten BB

Excel sheet © Fraunhofer

… even more (alternative) representations: Visio chart variants, XML, Scripts, …

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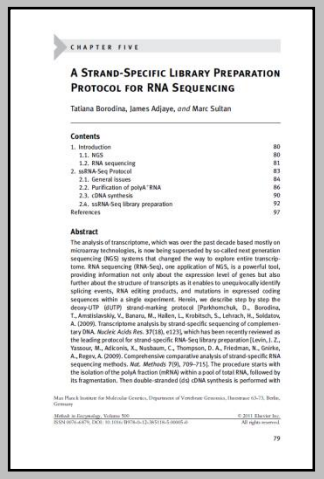
FLEXIBLE AUTOMATION
OUR APPROACH

Publication



CHAPTER FIVE

A STRAND-SPECIFIC LIBRARY PREPARATION PROTOCOL FOR RNA SEQUENCING

Tatiana Borodina, James Adjaye, *and* Marc Sultan

Contents

Abstract

The analysis of transcriptome, which was over the past decade based mostly on microarray technologies, is now being superseded by so-called next generation sequencing (NGS) systems that changed the way to explore entire transcriptome. RNA sequencing (RNA-Seq), one application of NGS, is a powerful tool, providing information not only about the expression level of genes but also further about the structure of transcripts as it enables to unequivocally identify splicing events, RNA editing products, and mutations in expressed coding sequences within a single experiment. Herein, we describe step by step the dexoy-UTP (dUTP) strand-marking protocol (Parkhomchuk, D., Borodina, T., Amstislavskiy, V., Banaru, M., Hallen, L., Krobitsch, S., Lehrach, H., Soldatov, A. (2009). Transcriptome analysis by strand-specific sequencing of complementary DNA. *Nucleic Acids Res. 37*(18), e123], which has been recently reviewed as the leading protocol for strand-specific RNA-Seq library preparation [Levin, J. Z., Yassour, M., Adiconis, X., Nusbaum, C., Thompson, D. A., Friedman, N., Gnirke, A., Regev, A. (2009). Comprehensive comparative analysis of strand-specific RNA sequencing methods. *Nat. Methods 7*(9), 709–715]. The procedure starts with the isolation of the polyA fraction (mRNA) within a pool of total RNA, followed by its fragmentation. Then double-stranded (ds) cDNA synthesis is performed with

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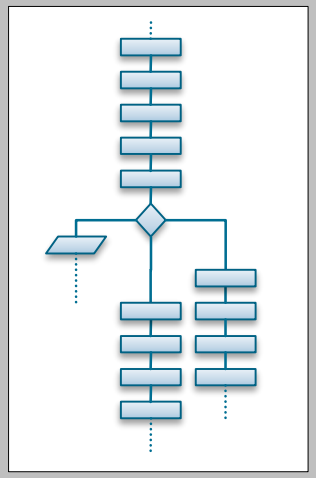
Prose Description
taken from
scientific and technical
literature

Abstract Model-based Representation

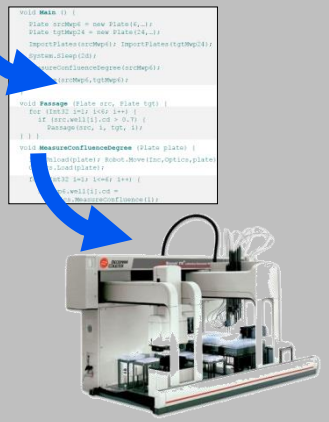


Abstract Description
of bio-technology processes
complete & sound w.r.t.
material flow, resource models, labware, substances,
and **properties of liquids**

OPC UA
SiLA
HZ INTERNATIONAL

standardized interfaces

Device Scripts (Hardware Level)



Library
of generic or specific
device-related scripts
based on
capabilities of
device control software

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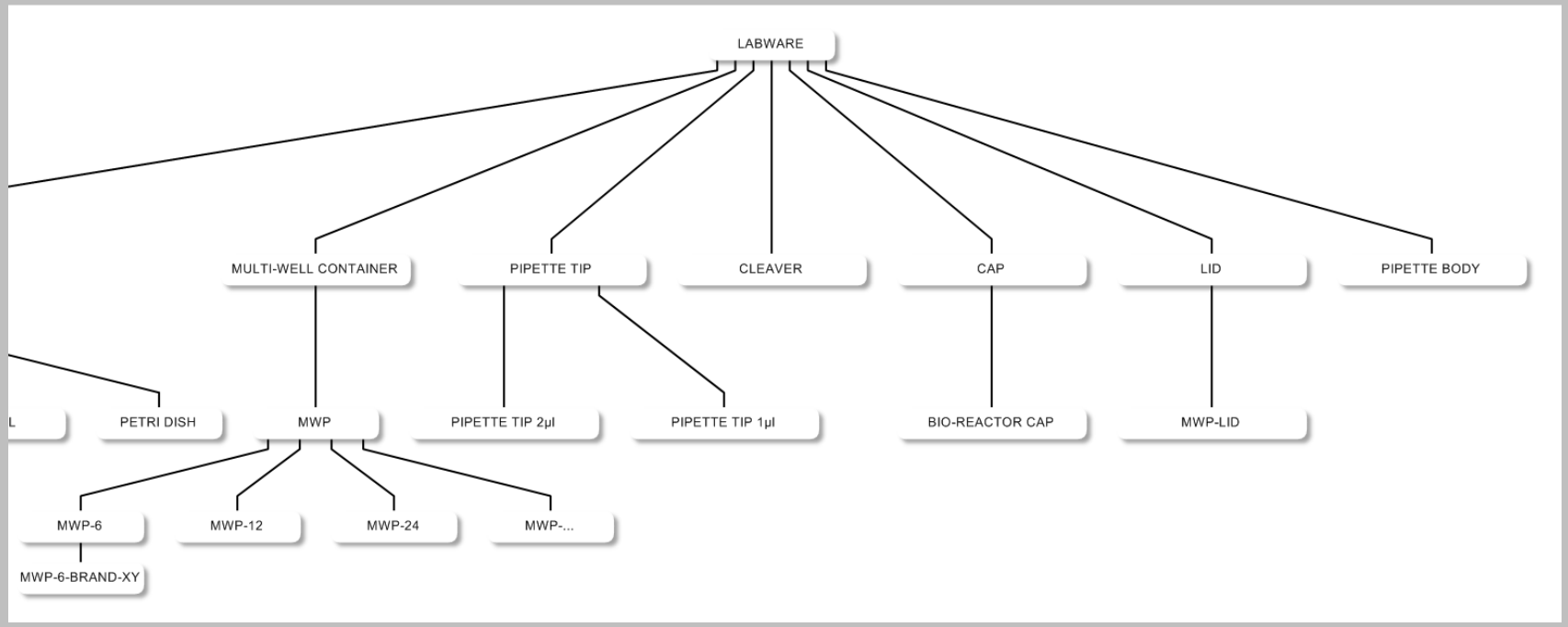
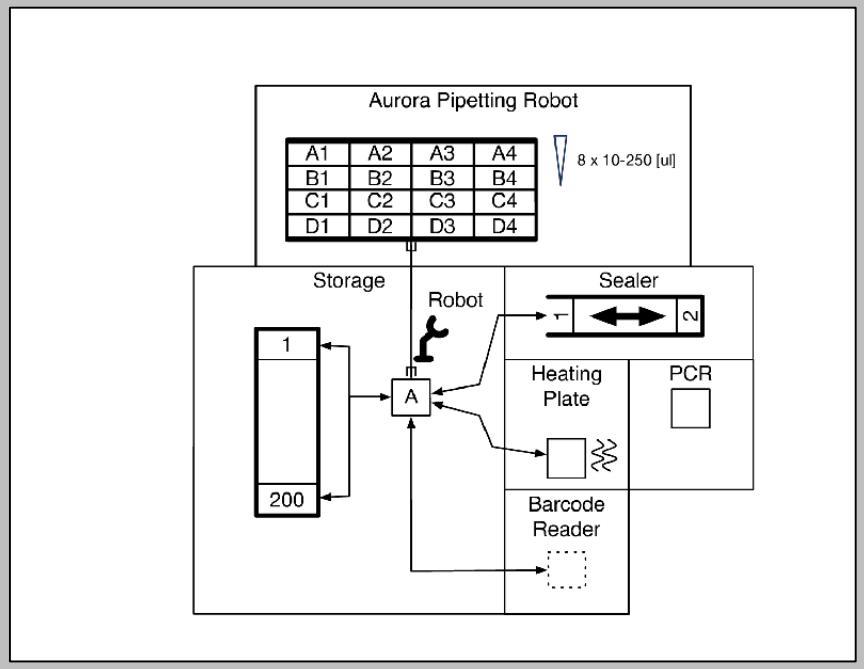
LABORATORY PROCESS MODELING NOTATION
USE OF ONTOLOGIES



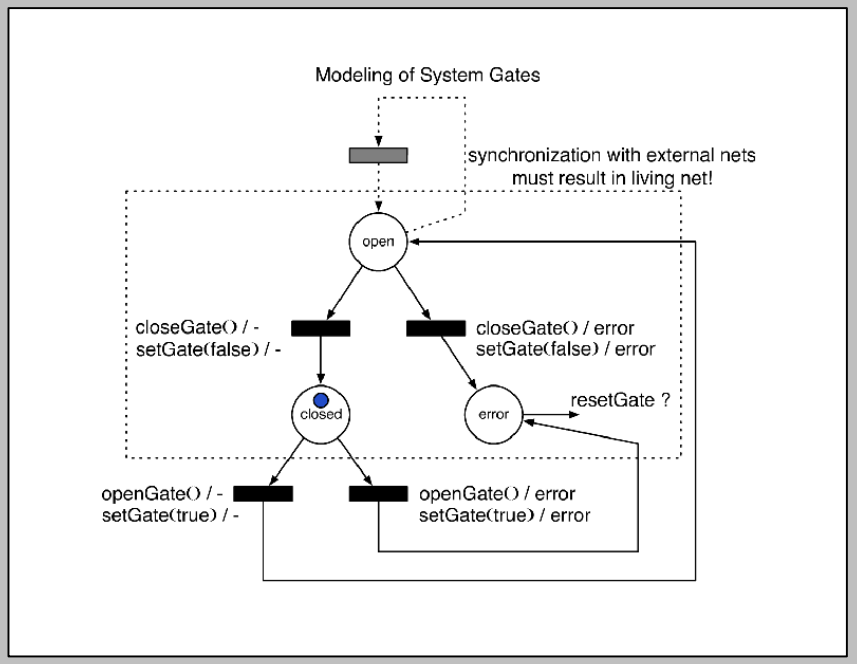
Ontology example (here: labware types, but also: substances and resources)

- unique type naming w.r.t. protocol collections
- inheritance hierarchy (e.g. induced by physical properties, …)
- equivalencies, e.g. “MTP-24” equals “MWP-24”

LABORATORY PROCESS MODELING NOTATION
RESOURCE MODELING



block diagram (locations, labware types, exchanges)



mathematical model (here Petri net model)

- Protocols require device interfaces, location, and “behaviors”
- Devices provide device interfaces, locations, and certain “behaviors”

- Process management system matches compatible protocols and devices

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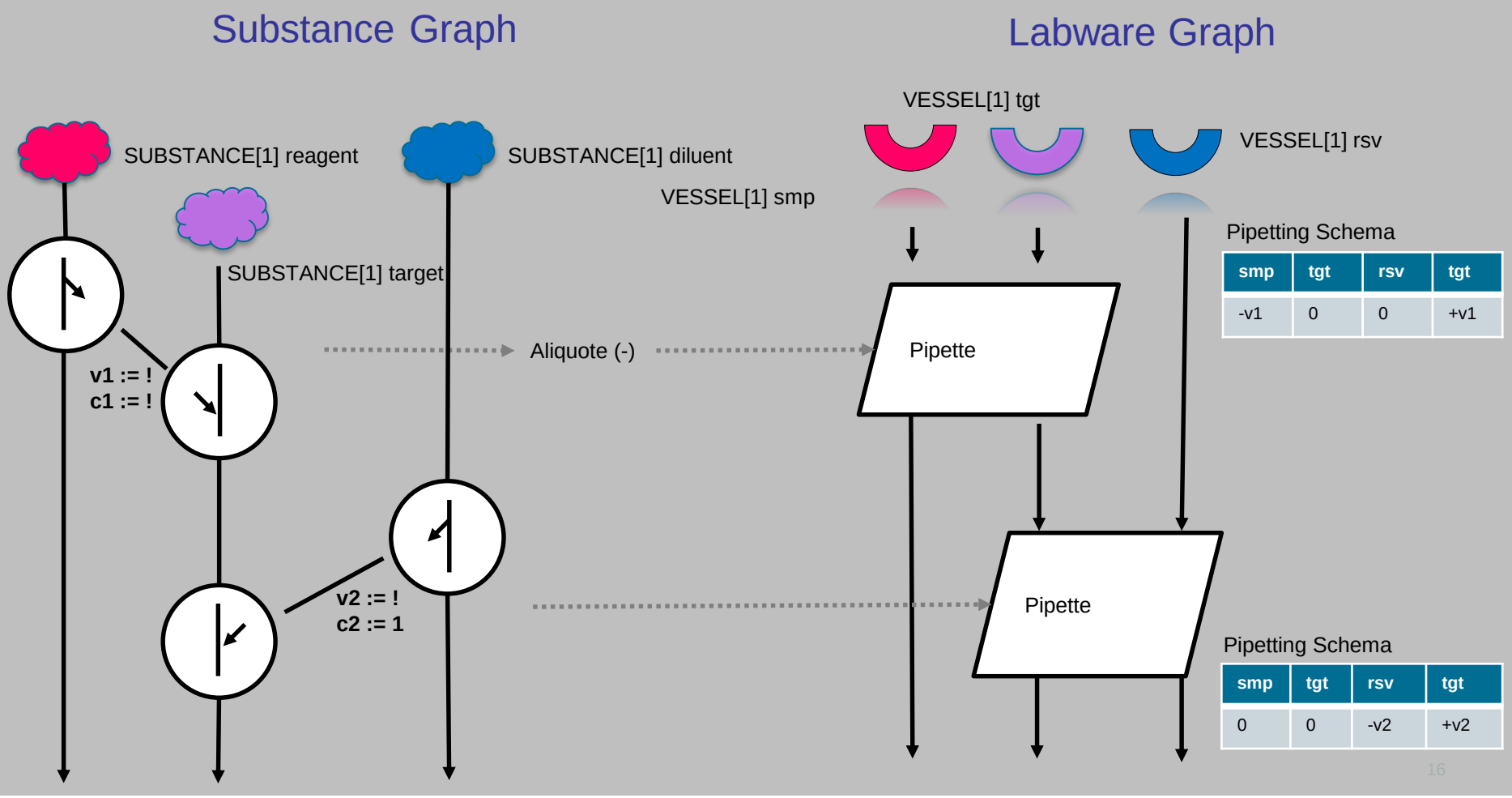
LABORATORY PROCESS MODELING NOTATION
EXAMPLE: 1-FOLD SEQUENTIAL DILUTION SERIES



v‘ := v1 + v2
c‘ := (c1 * v1) / v2

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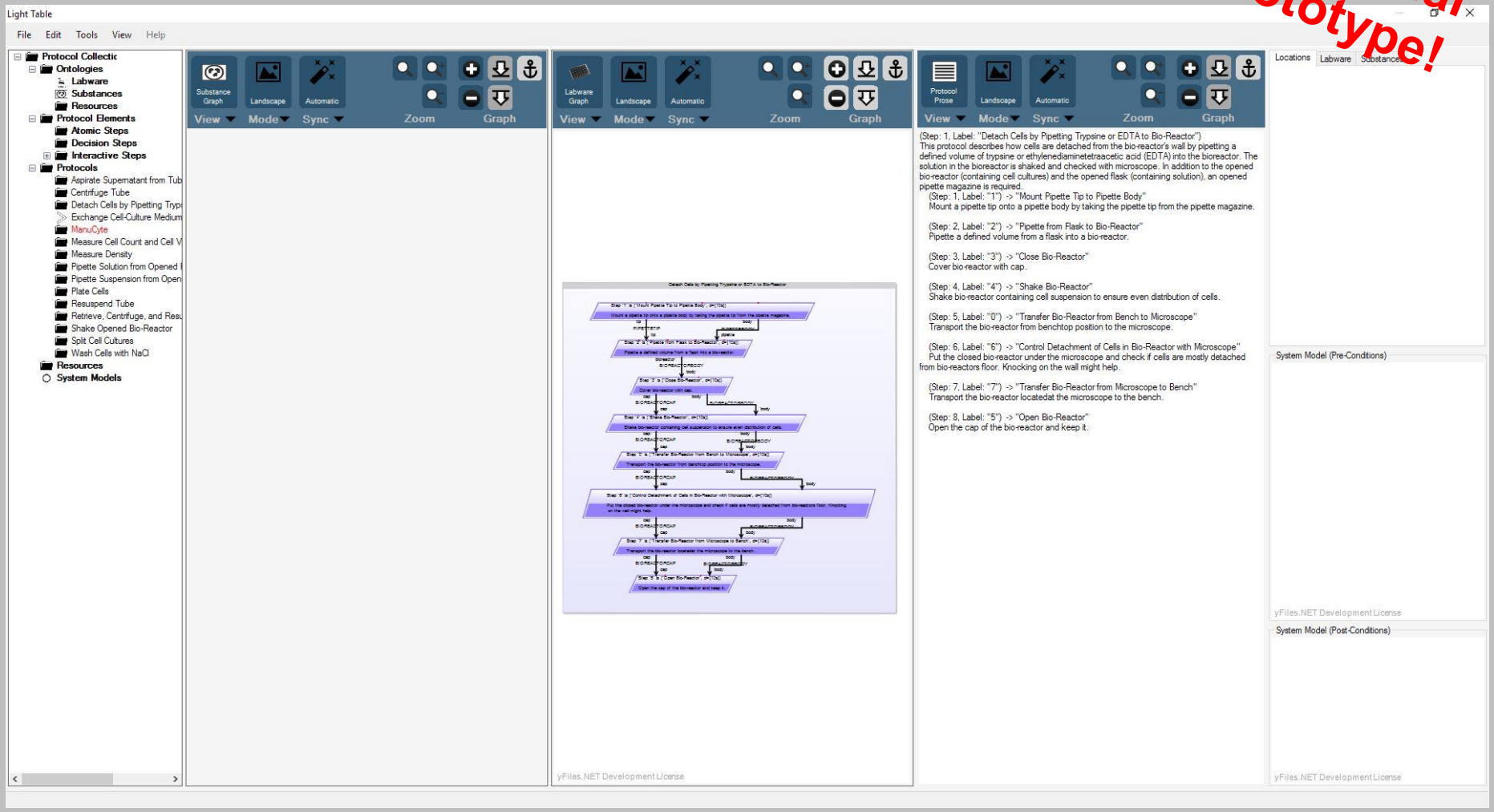
MERLIN PROTOCOL DESIGN

Functional Prototype!



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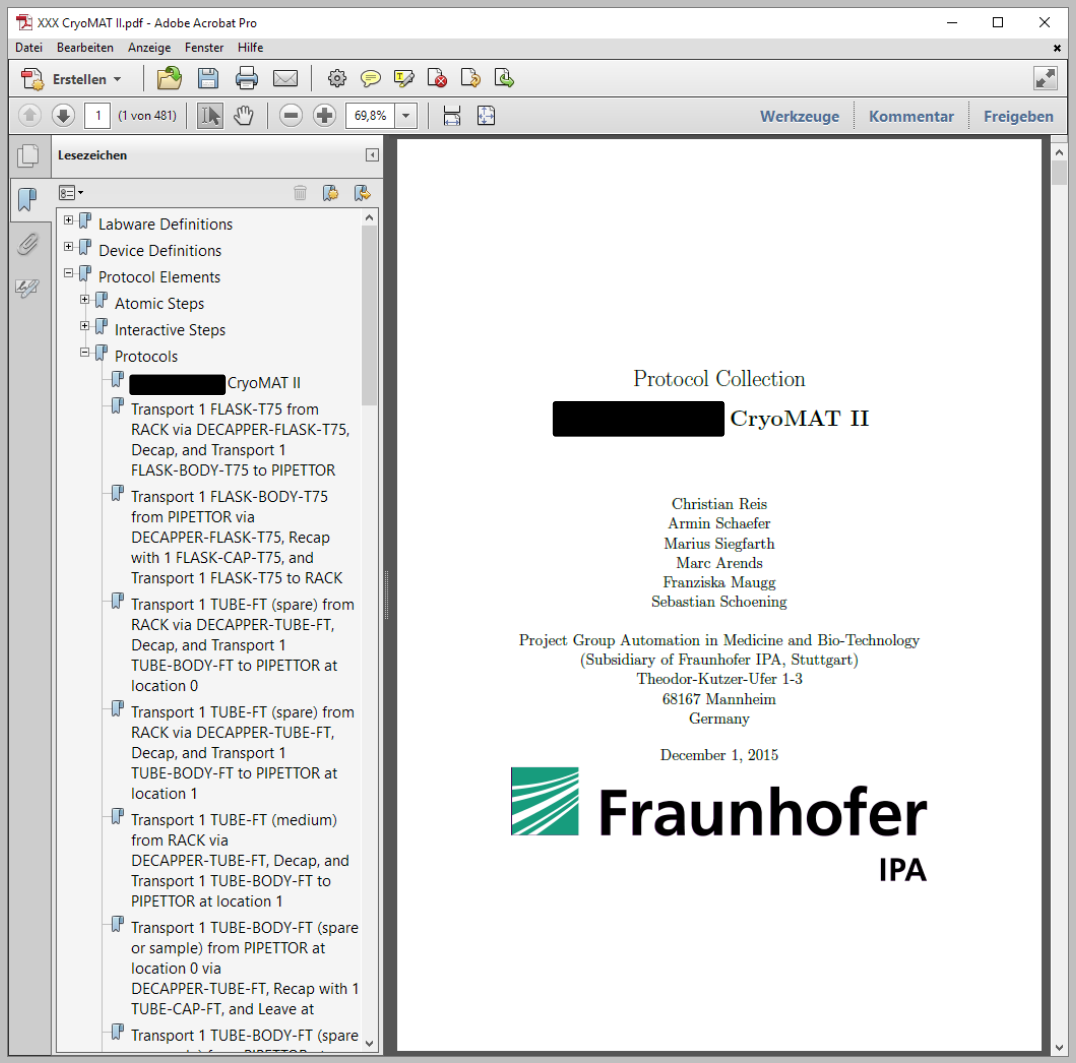
MERLIN PROTOCOL DOCUMENTATION



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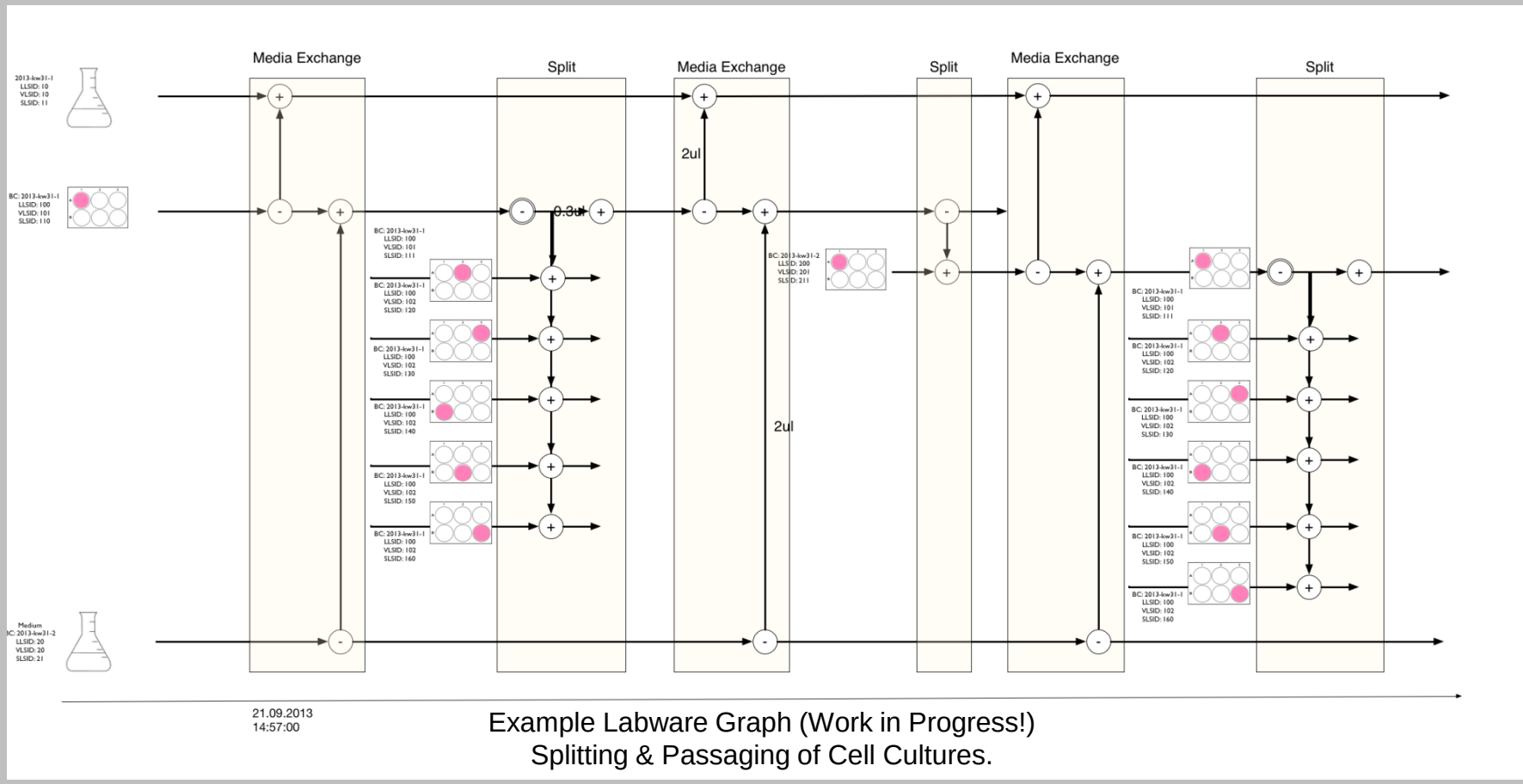
Process Execution

Consistent Labware and Sample Tracking & Scheduling



Example Labware Graph (Work in Progress!)
Splitting & Passaging of Cell Cultures.

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MERLIN MANUAL WORKFLOWS

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MERLIN SOFTWARE ARCHITECTURE

User Interfaces
(Merlin UI)

Protocol Bank
Data Management
Information Hub

Standardized
Protocol Definitions
& Device Scripts

ELN / LIMS

Process Management
(Merlin Core)

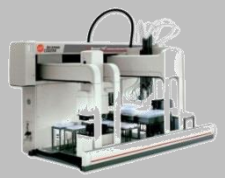
Commands
Parameters

Standardized Communication Interfaces

Control, Process,
Measurement
Data

Device Control

Device Control



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RERENCES LINKS

- http://www.flaticon.com/
- http://pamb.ipa.fraunhofer.de
- http://www.weg-von-der-insel.de