A NOVEL PROPOSAL TO ADVANCE THE DISCIPLINE AND TO QUANTITATIVELY SAFEGUARD IMPORTANT HYGIENIC BIO-PROCESSES

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ABSTRACT

A novel proposal that will significantly advance the discipline of chemical engineering, through an improved understanding of unanticipated process risk, and which will safeguard risk in hygienic bio-processing of foods, water and wastes is presented and illustrated. The proposal builds on established chemical engineering unit operations principles. If adopted by the discipline a major outcome would be to expand the current knowledge base and scientific understanding of process risk. This is because a key insight is to show that an accumulation and combination of a series of indiscernible changes in otherwise well-operated plant parameters can lead unanticipatedly in one-direction and leverage highly significant, and sometimes catastrophic, changes in process or product. Currently bio-process engineers are limited to largely ineffective sensitivity analyses or semi-quantitative assessments such as *HAZOP* (*HAZ*ard and *OP*erability), *HACCP* (*H*azard *A*nalysis *C*ritical *C*ontrol *P*oint) or *Reliability Engineering* (i.e. to "fail well"). Additional outcomes would include new technology and components to simulate the unanticipated risk of failure of hygienic processes in a novel library of risk-modules involving microbial growth and death. These new modules longer term will be able to be coupled with existing commercial design software for e.g. Aspen Plus® or Batch Process Developer® to provide significantly more powerful design and assessment techniques and tools than are currently used. These outcomes could then be used to quantitatively underpin new regulatory requirements for future bio-process plant and systems at the design, and operational stages and add intelligent and sophisticated new simulation capability to the discipline.

INTRODUCTION

The hygienic bio-processing of foods, pharmaceuticals, potable water and wastes is globally significant. Unanticipated failure of process or product in these areas is often catastrophic and has an enduring effect on public health and the economy, with or without fatality.

Currently there are four broad modes of risk assessment. A *Microbiological risk assessment* is clearly defined in the *Codex Alimentarius* (CAC 1998). However the lack of process is evident and often a "risk" is reported when what is actually meant is "hazard" (Thomas *et al* 2006; Whiting & Buchanan 1997). In food and pharmaceutical safety, *HACCP* (*H*azard *A*nalysis *C*ritical *C*ontrol *P*oint) is widely used and also mandated by regulation. It is a systematic, preventive approach that looks at physical, chemical, and biological hazards as a means of prevention, rather than finished product

inspection. A drawback is that there is no defined way, or template, as to how a plant should be inspected. Instead, each plant is required to create and implement their own *HACCP* system which they submit for regulatory approval. Results are often only semi-quantitative. In engineering *HAZOP* (*HAZ*ard and *OP*erability) study is well established but suffers from the fact that it is a qualitative technique based on guide-words. *Reliability Engineering* is a widely used capability to predict something to "fail well", that is, to fail expectedly and therefore without catastrophic consequences (O'Connor *et al* 2002). This notion is strongly connected to that of plant maintenance and understandable component life-cycle (British Standards Institution 1991).
Significant drawbacks with current risk assessments therefore include that they do not deal with quantitative assessment, or, do not provide insight into unanticipated and often catastrophic process plant failure. Because of this "human error" is widely blamed for unanticipated and catastrophic failure, or, sometimes "leaky" (faulty) surfaces or fittings are blamed, usually after exhaustive official hearings (Langer 2008; Cerf & Davey 2001). (This reasoning is actually less than convincing because these explanations themselves appear in need of explanation).
A new and quantitative understanding of process risk could therefore be used to advance the discipline of chemical engineering and be applied to quantitatively safeguard important hygienic bio-processes.

A New Process Risk Assessment

Davey & Cerf (2001) and Cerf & Davey (2003), Patil *et al* (2005) and Patil (2006) have demonstrated a novel application of Quantitative Risk Analysis with Monte Carlo simulation (QRA) to risk assessment of actual unit-operations in hygienic bio-processing, namely, sterilisation and fermentation. These are the most ubiquitous unit-operations globally. Importantly, they have presented findings as both quantitative and process-based. Their work has illustrated that QRA offers a powerful method for assimilating both *uncertainty* (i.e. the facts, or, level of ignorance) and *variability* (effect of chance) into a realistic appreciation of total risk in a process (Vose 2000). Whilst it is acknowledged this approach has been more recently applied by others, for example to simulating simple heating effects on bacterial death (Ferrer *et al* 2006), they have, as far as is known, single-handedly shown that standard chemical engineering unit-operations in chemical/bio-chemical bio-processes are amenable to QRA.
This work is opening up new opportunities for the discipline. It is based on the established practical notion that despite the best design and operation of plant a zero risk does not exist and there will be unanticipated failures. Davey & Cerf (2003) called this practically observable notion *Friday 13th syndrome*. The fact that this notion has persisted for so long in the industrial West suggests that it has observed time and again, in a number of variants (Suddath 2009).
Davey and co-workers have established that what, primarily, is required is a practical and unambiguous definition of failure of process or product in unit-operations. In hygienic bio-processing this is often the survival of unwanted pathogenic or spoilage contaminant microbes, or, the growth of competitor microbes.
A key insight of their work has been to show that an accumulation and combination of a series of indiscernible, but practically realisable, changes in otherwise well-operated plant parameters can lead unanticipatedly in one-direction and leverage highly

significant and catastrophic changes in process or product, for example, from sterile to non-sterile product, and; from stable to unstable operation (i.e. reactor "washout").
Because the approach is quantitative and based on principled mass and energy balances together with microbial kinetics that involve "whole-of-process" understanding, it is advantageous over more limited and current *HAZOP, HACCP, Microbiological risk assessments or Reliability Engineering* approaches. Currently bio-process engineers are limited to largely ineffective sensitivity analyses.
Moreover the published work has underscored that these currently used engineering risk approaches (i.e. single-value-best assessments plus sensitivity analyses) actually downplay the real risks of hygienic bio-process failure and contaminant survival (Cerf & Davey 2001; Patil *et al* 2005). That is, the true risk is actually significantly greater than can be currently assessed (Cerf & Davey 2001; Davey & Cerf 2003).
This is undesirable and has provided a strong motivation for the work on an improved understanding of risk.

A Novel Proposal

It is proposed that the demonstrated method pioneered by Davey and co-workers be used to produce practical, quantitative risk assessments of a wide range of individual bio-process unit-operations, and; to formulate these as a new library of chemical engineering risk modules.
Varying degrees of process model refinement would be possible. However, a common feature of each QRA risk module would be the identification and ranking of each of the key process parameters on likely plant and product failure(s). Application would be to quantitatively assess process risks associated with any targeted intervention strategies and any proposed changes to the physical plant.
The goal is a library of new risk modules based on sound chemical engineering unit-operations principles, that could be readily accessed and which could be readily applied to any stage of plant design or refit. The library would be a new assessment technology for the discipline that once established could be applied to a range of global hygienic bio-processes. A global process is defined as the integration of two or more of the new unit-operation risk modules (Davey, *unpublished data*).
This proposal is novel because it:

- Addresses the acute need to shift the present focus on semi-quantitative and qualitative assessments of risk, or life-cycle of components, to the significantly more practical "whole-of-process" understanding of unanticipated failure,
- Produces new and novel modules and technology and assessment techniques for risk assessments of hygienic bio-processes, and;
- Revolutionises practice in failure assessment and prediction in the bio-process industries by adding intelligent and sophisticated new simulation capability. This will permit design trials and intervention strategies to existing physical plant, characterised by any local features, to be quantitatively assessed.

Management and investigative and design work for bio-process safety would move from a largely qualitative and re-active, to a pro-active and quantitative, stance resulting in significant minimising of unanticipated problems of failure through a unique quantitatively-based understanding of inherent real risks.

A new and rapidly emerging, but less clearly defined, need for a quantitative, new risk assessment, is the necessary hygienic bio-processing and treatment of suspected, and possibly deliberately, contaminated bulk bio-agents, such as medical supplies or organic materials. QRA bio-security modules could be especially tailored for these applications.
Moreover, the proposal could be used to underpin a new Regulatory requirement for future bio-process plant and systems at the design, and operational, stages. Design and operation decisions will be made and assessed on a significantly better basis than is currently the case.
Once modules and techniques are developed for bio-process failure it should be possible to transfer the concepts to other areas in which failure can be clearly and unambiguously defined. One example of interest is the unanticipated and catastrophic failure of implants and prostheses.
The modules longer term should be able to be coupled with existing commercial design software for e.g. Aspen Plus® or Batch Process Developer® to provide significantly more powerful design and assessment techniques and tools than are currently used.

Advancing the Discipline

Major benefits for the discipline will be:

- New and science-based principles for a quantitative understanding of the inherent "true" risk in hygienic bio-processes that will expand the knowledge base,
- A library of tangible risk-modules that will make quantitative assessments of the safety of hygienic bio-process unit-operations involving microbial growth and death a practical reality,
- Ability to identify and rank key process parameters (such as exposure time and temperature or irradiation dose) as contributory causes in unanticipated failure,
- Capability to distinguish quantitatively the effect of targeted intervention strategies, including whether it is better to change "paired" key bio-process parameters (e.g. holding time and temperature) simultaneously, or separately, and by how much for each parameter,
- Guidelines on the level of refinement necessary for particular circumstances and integration strategies and pitfalls in simulation of global bio-processes, and;
- Potential for development of a new management tool for risk managers.

The discipline will advance current thinking from relatively simple, traditional risk and hazard applications to an elegantly simple (although mathematically quite complex), new risk assessment system.

A Practical Methodology

A conceptual framework that could guide the establishment of the proposal is presented below (Fig. 1). This shows how the interrelated concepts would be brought together. The framework integrates some significant components that are understood, e.g. unit-operations modules, and less-understood microbial kinetics, with those that will be newly developed, e.g. bio-security applications and the quantifying of expert knowledge, together with the QRA synthesis. Expert and anecdotal and other knowledge based on direct experience is actually compelling and should be drawn on (Cerf & Davey 2003).

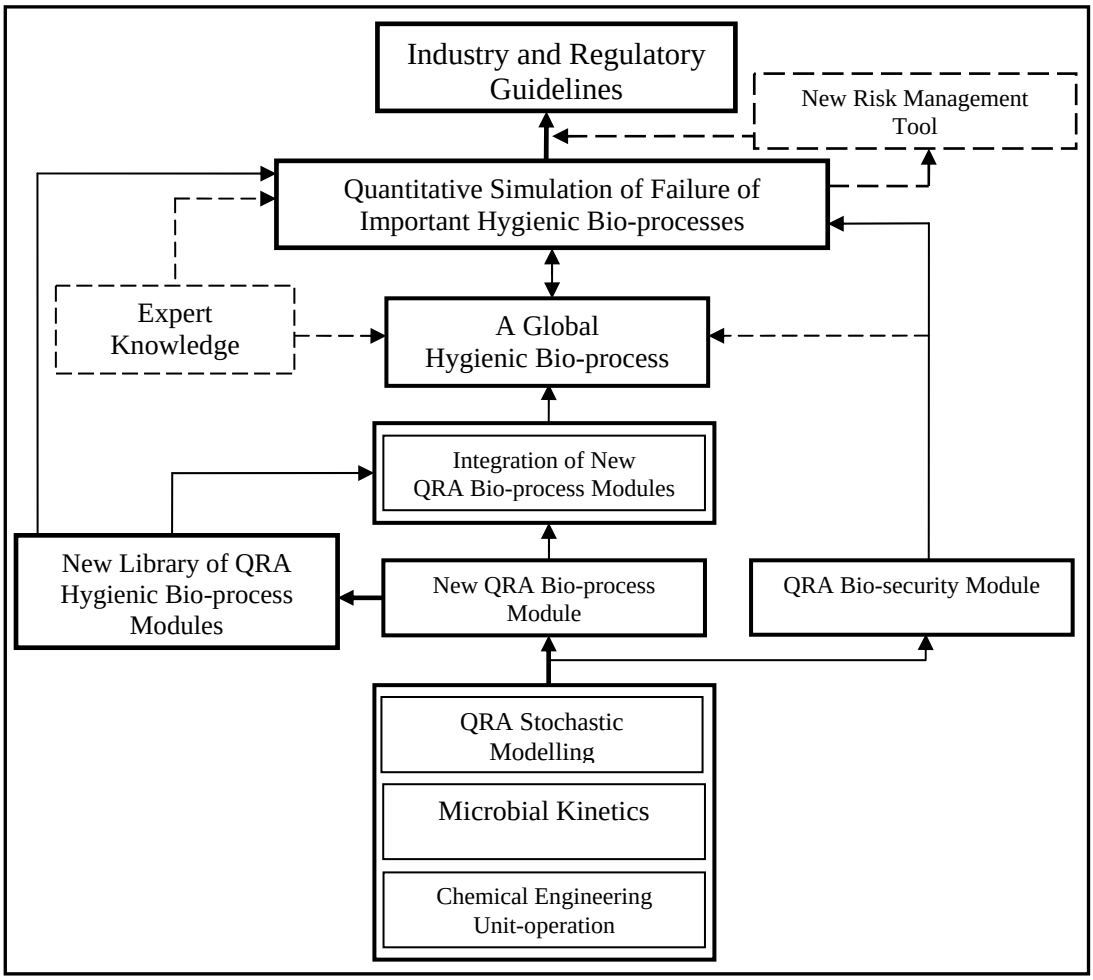

Fig. 1: Conceptual Framework for Proposal Establishment

The objective of the QRA is to calculate the combined impact of the *variability* (fact) and *uncertainty* (chance) in process parameters to determine a probability distribution of the possible process outcomes. Because traditional approaches do not separate these they cannot be used to gain insight into unanticipated bio-process failures. Current estimates of risk therefore appear safer than is in reality the case. This is actually, tacitly, acknowledged in that most current commercial operations involve deliberate and significant over-treatment. This of course is wasteful not only in energy, plant costs and volume, but importantly, in the number of undesirable side reactions that might take place. For thermal hygienic bio-processing of foods these can include the destruction of important proteins such as vitamins and enzymes that diminish the nutritional, sensory and other qualities of the product (Davey & Cerf 1996). By extension therefore, many claimed optimisation models of hygienic bio-processes will not currently be delivering on promises.

Because the QRA accounts for every possible value that each parameter may practically take and weights each possible "what if" with the probability of it actually occurring, the output results from the new modules will be a distribution of values, and not a single value. A number of outcomes will be defined as product or process failures. QRA therefore contrasts significantly with traditional engineering design approaches in which a single value for each input parameter is used and a single value output is given.

The numerical tasks can readily be automated using software that is commercially available e.g. @Risk (Palisade Corporation®) and Crystal Ball (Oracle®) (see for e.g. Cerf & Davey 2001). @Risk conveniently sits within engineering spread-sheeting such as Microsoft Office Excel.
Modules would be formatted to a standardised library style i.e. keeping them as general as practical. This should be readily facilitated because of the established nature of the underlying unit-operations basis. There nevertheless exists some scope on how this might actually turn out.
In the bio-process industries unit-operations can fit into any of six major classes (Katoh & Yoshita 2009):

- Heat Transfer,
- Mass Transfer,
- Bioreactors,
- Membranes Processes,
- Cell-liquid Separation and Cell-disruption,
- Sterilization, and;
- Adsorption and Chromatography.

A 5-Step Algorithm

A 5-step algorithm identified Davey and co-workers (e.g. Davey & Cerf 2003) could be used, namely:

1. Select an identifiable hygienic bio-process class and unit operation:
   a. Synthesize and validate mass and energy balances and microbial kinetics as key process parameters in a suitable computational model and software for particular plant throughputs,
   b. Establish a clear definition(s) of product failure.
2. Identify key process parameters on product failure(s) using traditional engineering, single-value-assessment approaches.
3. Derive, investigate and test plausible probability distributions for key process parameters.
4. Simulate process operation and likely product failures using new quantitative-risk-assessment (QRA) approaches:
   a. Identify and rank the significance of the key process parameters on product failure(s),
   b. Investigate effects of "what if" scenarios and consequences of proposed intervention strategies. Evaluate risks and potential opportunities.
5. Distil insights from QRA into advice for minimising risk and improving plant operation.

As highlighted in Fig. 1 some input values may need to be derived from expert knowledge or, from expertise with particular processes or, the fitting of input-distributions to fragmented literature data, as demonstrated by Cerf & Davey (2001) who successfully used principles of flow regimes and velocity distributions to scope data.

A Prioritised Approach

A prioritised approach could be that through industrial relevance of the particular bio-processes of interest. The most widely used unit-operation globally is bulk sterilisation (of liquid, media, air etc). The UV irradiation for potable water production and preparation of fermentation media and equipment and bulk heating and cooling and recovery of waste heat as an economic measure, are also very widely used. These are "core" operations in many bio-processes.

This means that modules, components and techniques developed for these can be used in a number of processes. These processes are also particularly important to Australia as a major food exporter and centre of water expertise and specialist pharmaceutical producer.

The library of modules will be progressively established. In principle, any hygienic bio-process with two or more identifiable unit-operations and which can be represented by a typical block flow diagram or flow-sheet can be targeted.

Probabilities of unanticipated events that will lead to failure of product or plant will be determined using numerical simulations. Of course, this same process will also be applied to "opportunities" i.e. those events that have some probability of occurring, but which would be of benefit should they do so. Risk and opportunity should be considered as opposite sides of the same coin.

Module validation will necessarily involve extensive calculations. "Pure" Monte Carlo sampling has a serious drawback. In the author's experience it can both over- and under-sample from various parts of the distribution. Therefore it simply cannot be relied on to replicate the input distribution (unless a very, very large number of iterations are carried out). Latin Hypercube Sampling should therefore be used as a much better option. This uses a *stratified sampling without replacement* (Vose 2000). In practice this means the random sampling of each probability distribution within a parameter to produce 1000's (or more usually 100,000's) of scenarios (iterations or trials) covering the entire range of the distribution. With this modification the QRA simulation will have a number of advantages:

- The distributions of the model's parameters do not have to be approximated in any way,
- Correlation and other inter-dependencies can be modelled,
- The level of mathematics required to perform a simulation remains basic,
- The computer does all the work in determining the outcome distribution,
- The tasks involved in the simulation are automated,
- Complex mathematics can be included (e.g. power functions, logs, IF statements, etc.) with no extra difficulty and can be used to integrate otherwise intractable mathematical functions,
- The technique is widely recognised as valid so its results are more likely to be accepted by practitioners,
- The behaviour of the model can be investigated with ease, and;
- Changes to the model can be made very quickly and the results compared with previous models.

The simulator uses a random number generator. There are many algorithms that have been developed to generate a series of random numbers between zero and one with equal probability density for all possible values. Vose (2000) can be consulted for a thorough review of the basis for these.

Internationally important hygienic bio-processes of particular interest are the:

- Aseptic upstream processing and downstream packaging of bulk liquid foods,
- Clean-in-Place (CIP) systems for foods and pharmaceutical plant and equipment,
- UV irradiation for potable water production,
- Irradiation of single-use medical devices (such as surgical gloves and syringes), and;
- Process options and risk of treatment failure for possibly deliberately contaminated bulk bio-agents (such as medical supplies or organic materials).

The proposed new module output will include a quantitative ranking of the contributing causes of each input parameter to risk and consequent "best " intervention strategy i.e. what is better, say in thermal sterilisation, to increase process temperature (what maximum is possible with the existing physical equipment?), or time (can this be changed easily?), or, to change temperature-time together (and by how much?).

The resulting improved and quantitative appreciation of the importance of key process parameters defined carefully through both *fact* and *chance* will enable a more informed understanding of the relationship between bio-process operation and failure than can be obtained with current methods.

DISCUSSION

The notion of variability used in QRA analyses contrasts with that of almost entrenched engineering *determinism* i.e. the view that an omniscient machine could predict any future event based on a full understanding of the present. It is acknowledged therefore that some practitioners cannot accept that variability (*chance*) will play a part, or even a significant part, in the failure of bio-process plant and product, and that its effect cannot be minimised through yet more measurements i.e. "facts" about the process (Vose 2000). Variability needs to be understood as simply a function of any real process system, especially hygienic bio-processing operations. It does not suggest that "God does play with dice".

Although risk programs have been very recently established in both Australia and France for e.g. *The Australian Centre of Excellence for Risk Analysis*, in the School of Botany, The University of Melbourne (established 2006) and; *Met@risk*: *Methods for Food Risk Analysis*, l'Institut National de la Recherche Agronomique, Paris (created 2004), the work emphasis is not on unit operations or whole-of-process but primarily on "hazards" for, respectively, "import clearance", "response actions for invasive species" and "decision making in complex systems", and; "human dietary exposure" and "socio-economic analyses of regulatory measures". Further, no independent workers around the world currently working on risk assessments e.g. Ferrer *et al* 2006; Min & Choi 2009; Gudmundsson & Kristbergsson 2009, as far as is known, have taken the crucial step of linking the microbial aspects with aspects of process using quantitative risk assessments in chemical/bio-chemical engineering unit operations as is being proposed here.

It has been shown by Davey and co-workers that unanticipated and often catastrophic failures in hygienic bio-processing can be quantitatively analysed, and; appropriate intervention strategies can be developed and tested to safeguard process risks. The discipline should capitalise on the proposal to extend this work to a wide range of standard, unit-operations and the establishment of a new library of risk modules that could be used to advance the discipline and underpin plant and process safety.

CONCLUSIONS

A novel proposal for development of a new assessment of process risk has been outlined. Adoption by the discipline of the proposal through a suggested establishment methodology will:

1. Significantly advance the discipline of chemical engineering through an improved understanding of process risk that builds on established unit-operations principles,
2. Create in a timely fashion a library of new quantitative risk modules that will expand the knowledge base and be an important discipline resource that will be difficult to replicate elsewhere,
3. Add intelligent and sophisticated new simulation capability to the discipline to safeguard important hygienic bio-processes and products through new and practical methodologies for quantitative assessment of process risk and intervention strategies.

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